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# Role of Choroidal Thickness and Cataract Surgery in the progression of Geographic Atrophy

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**Mestrado Integrado em Medicina**

**Área: Oftalmologia**

**Trabalho efetuado sob a Orientação de:**
**Dr. Manuel Falcão**

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# Role of Choroidal Thickness and Cataract Surgery in the progression of Geographic Atrophy

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## Keywords

geographic atrophy; cataract surgery; choroidal thickness; age-related macular degeneration; phacoemulsification

## Abstract

**Purpose:** To examine the relationship between geographic atrophy (GA) progression and choroidal thickness (CT) and cataract surgery.

**Methods:** Previously recorded Fundus Autofluorescence (FAF) and Spectral-Domain Optical Coherence Tomography (SD-OCT) images of patients with GA were analysed and GA area and choroidal thickness were measured in different moments in time. Subfoveal CT was measured in all eyes and in those with the largest lesion outside the fovea an additional measurement was made at the centre of the lesion. GA area progression and CT progression were calculated based in these measurements. The eyes were then divided in three groups according to their phakic status: pseudophakic, surgery performed during the study and phakic. Statistically significant differences between these groups in GA area progression were calculated. Differences in GA progression in the second group before and after surgery were also analysed.

**Results:** Median and mean GA progression rates in the three groups were 0.05/0.10; 0.13/0.13 and 0.08/0.11 mm2/month respectively (p=0.154). In the patients intervened during the study, mean GA progression rates before and after surgery were 0.09±0.12 mm2/month and 0.08±0.06 mm2/month respectively (p=0.874). We found no association between initial subfoveal CT or initial largest lesion CT and GA progression (p=0.139; p=0.910).

**Conclusion:** We found no association between geographic atrophy progression and choroidal thickness or phakic or pseudophakic status.

## Introduction

Age-related Macular Degeneration (AMD) is a leading cause of blindness worldwide especially in developed countries. It affects primarily older patients, and is divided in a "wet" and "dry" form due to different manifestations and prognosis. (Ambati and Fowler 2012, Erke, Bertelsen et al. 2012, Owen, Jarrar et al. 2012)

Geographic atrophy (GA) is the end-stage of dry AMD. Its hallmark is a progressive degeneration of the retinal pigment epithelium (RPE) and photoreceptors. (Gobel, Fleckenstein et al. 2011, Ambati and Fowler 2012, Bhutto and Lutty 2012) Although its course is not as fast as in wet AMD, GA can cause some degree of visual impairment and evolve to severe central blindness, being responsible for 10% of legal blindness attributed to AMD. (Ambati and Fowler 2012, Zhou, Ye et al. 2012) Contrary to wet AMD, there is currently no treatment for geographic atrophy in a form capable of clearly reversing or slowing the progression of the lesions or reversing the symptoms. (Nowak 2006, Ambati and Fowler 2012, Kanagasingam, Bhuiyan et al. 2014)

Fundus autofluorescence (FAF) imaging is a non-invasive imaging method that allows topographic mapping of lipofuscin distribution in the RPE cell monolayer in-vivo. Due to the absence of RPE lipofuscin, atrophic areas in eyes with GA have a severely reduced signal. Using image software it is possible to quantify the area of GA and analyse the progression of the lesions. (Gobel, Fleckenstein et al. 2011, Schmitz-Valckenberg, Brinkmann et al. 2011, Khanifar, Lederer et al. 2012, Kanagasingam, Bhuiyan et al. 2014)

The understanding of the underlying mechanisms of disease is far from complete and several theories have been proposed. (Nowak 2006, Ambati and Fowler 2012, Bhutto and Lutty 2012, Parmeggiani, Romano et al. 2012, Zhou, Ye et al. 2012, Coleman, Silverman et al. 2013) Genetics most certainly plays an important role, as well as environmental factors such as smoking. (Fraser-Bell, Wu et al. 2006, Nowak 2006, Ambati and Fowler 2012, Parmeggiani, Romano et al. 2012)

Cataract is the most common ophthalmologic disease of elderly people. It is characterized by "blurred" vision caused by opacity of the crystalline lens due to its degeneration accompanied by water and elasticity loss. (Bockelbrink, Roll et al. 2008, Chew, Sperduto et al. 2009, Casparis, Lindsley et al. 2012)

Phacoemulsification with intra-ocular lens implantation is one of the most performed surgeries, consisting of the removal of the opacified lens and replacement by an artificial lens implant. (Cugati, Mitchell et al. 2006, Bockelbrink, Roll et al. 2008, Casparis, Lindsley et al. 2012, Wang, Fong et al. 2012)

Some previous studies suggested a relation between cataract surgery and the progression of AMD, while others found no such association. (Cugati, Mitchell et al. 2006, Bockelbrink, Roll

et al. 2008, Chew, Sperduto et al. 2009, Fraser-Bell, Choudhury et al. 2010, Casparis, Lindsley et al. 2012, Wang, Fong et al. 2012, Zhou, Ye et al. 2012)

The choroid is a vascular layer of the eye that lies beneath the retina. It is responsible for the vascular supply of the outer retina, including the RPE. (Ikuno, Kawaguchi et al. 2010, Manjunath, Goren et al. 2011)

It has been previously proposed that choroid might play a role in the development of AMD, but the matter remains controversial. (Ikuno, Kawaguchi et al. 2010, Manjunath, Goren et al. 2011, Bhutto and Lutty 2012, Coleman, Silverman et al. 2013)

With the use of Spectral-Domain Optical Coherence Tomography (SD-OCT), especially using the Enhanced Depth Imaging technique it is now possible to obtain detailed, images from the choroid allowing its measurement. (Spaide, Koizumi et al. 2008, Gobel, Fleckenstein et al. 2011, Manjunath, Goren et al. 2011, Kanagasingam, Bhuiyan et al. 2014)

Because cataract surgery is a frequent procedure in patients with dry AMD it is important to understand its effects and those of intra-ocular lens implantation on the progression of the geographic atrophy. We also correlated progression of geographic atrophy with choroidal thickness.

## Methods

This retrospective study analysed patients that are being followed in the Retina Department of our hospital and are being followed by autofluorescence and SD-OCT.

In our department, patients with geographic atrophy are imaged using the Spectralis® Heidelberg® that allows the acquisition of both fundus autofluorescence and SD-OCT. SD-OCT and FAF images recorded in routine clinical practice were retrospectively analysed using the Heidelberg SPECTRALIS® Software.

We selected patients' eyes that had at least 2 images and at least 6 months of follow-up. Exclusion criteria included: areas of geographic atrophy larger than the square that can be obtained from the spectralis® AF image, aphakic status, presence of other retinal disease such as wet AMD or diabetic retinopathy.

To measure the GA area, Region Finder™ (Heidelberg Engineering) software was used. With this software atrophic areas are outlined on the screen using the mouse-driven cursor. The software allows a direct export of FAF images from the database, semi-automated detection of atrophic areas by shadow correction, vessel detection, selection of seed points and comparison of images from the same patient. (Gobel, Fleckenstein et al. 2011, Schmitz-Valckenberg, Brinkmann et al. 2011) The software then compares the sequential images for each patient and automatically calculates the selected areas and calculates growth rates.

Choroidal thickness measurements were performed manually by the same single observer (MT) using the calipers provided by the Spectralis® Heidelberg® software. Choroidal thickness

was measured from the outer limit of the retinal pigment epithelium to the choroidal-scleral junction. A single vertical measurement was made under the fovea. When the largest lesion was not on the fovea, an additional measurement was also made under the centre of the largest lesion.

Data from each patient regarding the phakic status of each eye (phakic versus pseudophakic) was obtained from the patients' medical records. All patients that had previous cataract surgery were labelled pseudophakic, and patients that had not had any cataract surgery were considered phakic.

The eyes were then divided in three groups according to their phakic status: pseudophakic, surgery performed during the study and phakic. Statistically significant differences between these groups in GA area progression were calculated. Differences in GA progression in the second group before and after surgery were also analysed. Statistical analysis was performed using Student's t-test, paired sample *t*-test, one-way Anova and Pearson's correlation coefficient. Data normality was calculated using Shapiro-Wilk test. For non-normal data the Kruskal-Wallis and Mann-Whitney tests were used. Statistical significance was considered when $p < 0.05$.

## Results

The initial database contained a total of 118 eyes from 59 patients. Of these eyes, 56 (47%) were included and 62 (53%) excluded from this study. The exclusion criteria were the following: lack of the necessary number of images in 32 eyes (27%); presence of wet AMD in 18 (15%); no evidence of GA lesions in 5 (4%); other ophthalmologic lesions in 4 (3%) and lesions larger than window size in 3 eyes (3%).

Of the 56 accepted eyes, 17 were pseudophakic; 35 phakic, and 4 were submitted to surgery during the study allowing a comparison of the progression rate of GA before and after the procedure. The mean age of the patients was 82±6 years. 26 (46%) eyes were from male patients and 30 (54%) from female ones.

35(63%) patients had bilateral GA; 12(21%) had wet AMD in the fellow eye and 9(16%) had no advanced AMD in the fellow eye. The status of the fellow eye had no relation with the GA progression rate ($p=0.447$; Kruskal-Wallis).

10 eyes had two measurements included, 25 had 3 and 21 had four images, resulting in a mean of 3.20 images per eye.

In 37(66%) eyes the largest lesion was over the fovea while in 19(34%) it was not (Table 1).

The mean period between the first and last image was 25±12 months. At the first image the mean GA area (Table 2) was of 5±6 mm2, the mean subfoveal choroid thickness (CT) was 175±66 μm and the mean CT under the largest lesion was 183±67 μm. At the last image the

mean GA area was 7±7 mm2, the mean subfoveal CT was 157±63 µm and the mean CT under the largest lesion was 182±80µm.

Subfoveal choroidal thickness in the first and last images had a weak inverse relation with patient age (p=0.026, r= -0.298; p= 0.043, r= -274, Pearson correlation test).

In relation to the first image, mean GA area variation was 114±160 % mean subfoveal CT variation -8±20% (range -50; 54), and mean CT under the largest lesion -7±34%

The median in GA area progression rate was 0.07 (range: 0.00-0.44) mm2/month; mean subfoveal CT progression rate was -0.85±3 µm/month and mean CT progression under the largest lesion was -0.48±3 µm/month.

The relation between initial subfoveal CT or initial largest lesion CT and GA progression was not statistically significant (p=0.139; p=0.910, Pearson correlation test). There was no statistically significant difference in GA progression between the eyes with foveal or extra-foveal lesions (p=0.979, Mann-Whitney).

Regarding the three groups of surgery status (pseudophakic, surgery during the study or phakic), the mean ages were 84, 86 and 80 years. In the first category 6 eyes had the largest lesion over the fovea and 11 did not, this changed to 3/1 and 28/6 in the other categories. The mean follow up periods were 22±3; 32±8 and 25±2 months respectively. The difference in GA progression between these groups was not significant (p=0.154, Kruskal-Walis). (Tables 1 and 2)

In the 4 eyes intervened during the study, the mean GA progression rate was 0.09±0.12 mm2/month before cataract surgery and 0.08±0.06 mm2/month after (Table 3). We found no statistically significant difference in the progression rate of GA before and after the surgery (p=0.874, paired sample T-test).

## Discussion

Several mechanisms and risk factors have been suggested for the development of GA. (Fraser-Bell, Wu et al. 2006, Fraser-Bell, Choudhury et al. 2010, Ambati and Fowler 2012, Parmeggiani, Romano et al. 2012, Zhou, Ye et al. 2012, Coleman, Silverman et al. 2013) A particular attention has been paid to the role of cataract surgery given that cataracts and AMD are two of the most common ophthalmologic diseases, especially in the ageing populations. At this point, there is no clear association between cataract surgery and the progression of AMD (Casparis, Lindsley et al. 2012).

Our study found no association between geographic atrophy progression rate and phakic status. We analysed this association by a group of patients previously submitted to cataract surgery with phakic patients and also by comparing progression rates before and after surgery in the group submitted to phacoemulsification during the study. Both results were consistent with the absence of a worsening of GA provoked by cataract surgery. This is an additional step in the

argument against the proponents of a positive association between phacoemulsification with intra-ocular lens implantation and AMD (Cugati, Mitchell et al. 2006, Fraser-Bell, Choudhury et al. 2010) and in favour of those who find no association (Chew, Sperduto et al. 2009, Wang, Fong et al. 2012).

Other studies have also suggested that the problem could be not cataract surgery, but that the cataract itself had protective effects either by providing protection against deleterious sun light, which has a controversial role in AMD progression, (Cruickshanks, Klein et al. 1993, Delcourt, Carrière et al. 2001, Fletcher, Bentham et al. 2008, Yam and Kwok 2013) or by the presence of αA-crystallin (Zhou, Ye et al. 2012). In both cases the removal of the cataract and thereby removal of the protective mechanism should increase GA progression which was not observed in our study. Even though in our retrospective study, we did not quantify the crystalline status of the phakic population, with a mean patient age of 82 years, some degree of lenticular opacification is expected. Therefore, a protective effect of the cataract, if present, should have been observed.

Even though the number of eyes submitted to surgery during the study was small (4 eyes), we could not find a significant difference in the GA progression rate before and after the procedure, or any acute retinal or choroidal change detectable on SD-OCT.

A difference between this study and most of the previous is its focus on patients already with a late stage manifestation of AMD and not in the progression from early stages to late stages of AMD.

This was relevant because we did not find an association between phakic status and GA progression. This may mean that it is probably safe to have cataract surgery on patients with GA. In our four eyes that had surgery during the study period we did not find any cases of acute retinal or choroidal changes caused by the surgery and we did not find any changes in GA progression. Even though cataract surgery may not improve visual acuity when the fovea is compromised by GA, other benefits of cataract surgery such as improved contrast sensitivity may improve the quality of life of these patients without compromising the retinal disease.

Furthermore a mean time between first and last images of 25 months and a mean of 3.2 pictures per eye allowed us to observe important patterns in lesion progression.

It is possible that in these older patients with advanced disease the effects of lens removal are different from younger early stage patients. Likewise, we had no access to data of lesion progression before the surgery in the group of patients operated before the beginning of the study which could have provided further useful information about GA and CT progression rates.

In this study we also tried to examine the relation between GA progression and CT as it had been suggested that choroidal dysfunction could be related with AMD (Coleman, Silverman et al. 2013, Sigler and Randolph 2013). Similarly we found no supporting evidence for these hypotheses as both baseline subfoveal CT and largest lesion CT were not associated with any

change in GA progression. This was true for all the three groups. As a consequence we cannot support the role of CT as cause or a marker of GA progression. However, choroidal abnormalities that cannot be detected by SD-OCT may play an important role in GA progression.

An interesting finding regarding the choroid was a mean change in subfoveal choroidal thickness of –8 % and of -7% in largest lesion CT in a mean period of only 25 months. Even though this was not a uniform tendency, with 16 eyes out of 56 showing an increase in subfoveal CT and 5 out of 17 in largest lesion CT, to our knowledge it is the first time such a significant choroidal thinning in a relatively short period is described. The implications of this are at the moment unknown. The reduction in choroidal thickness could either be a consequence or a cause of GA progression; or it might not even be related.

This study had some important limitations. Its retrospective nature, with restraints in the available data, and the small number of eyes submitted to surgery during the study were the most relevant. Data regarding sun light exposure, anti-oxidant intake and smoking was not accessible and would have been important in controlling biases. The reduced number of eyes undergoing phacoemulsification with the required number of images may be partly due to the SD-OCT and autofluorescence imaging being available only in 2009. Further studies will accordingly be able to include more patients allowing stronger conclusions.

Although we could not identify any predicting factor of GA progression and found no association with cataract surgery we acknowledge the need for further investigation in this area with a higher number of individuals included, and taking into account a larger number of relevant variables as those above mentioned. The used method of analysing several sequential images of the same eye may be particularly indicated as it allows differentiation between natural disease progression and influence of external factors.

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## Tables

| Table 1 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Phakic Status** | | | | | | | | | |
| | Pseudophakic | | | S. during the study | | | Phakic | | | Total |
| Eyes, n | 17 | | | 4 | | | 35 | | | 56 |
| Gender | 6M | | 11F | 1M | | 3F | 19M | | 16F | 56 |
| Fellow-eye AMD | 5N | 10GA | 2W | 0N | 2GA | 2W | 4N | 23GA | 8W | 56 |
| LL out of Fovea (n) | 11 (65%) | | | 1 (25%) | | | 7 (20%) | | | 19 (34%) |

Table 1: Number of eyes, gender, status of the fellow eye and largest lesion outside the fovea, by phakic status. M: male, F: female, AMD: age-related macular degeneration, N: No AMD lesion, GA: geographic atrophy, W: wet AMD, LL: largest lesion; S: Surgery.

| Table 2 | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Phakic Status** | | | | | | | | | | | | | | |
| | Pseudophakic | | | | | S. during the study | | | | | Phakic | | | | |
| | Min | Max | Mean | Med | stDv | Min | Max | Mean | Med | stDv | Min | Max | Mean | Med | stDv |
| GAA first image (mm2) | 0.1 | 16.3 | 5.4 | _ | 5.7 | 2.5 | 6.3 | 4.3 | _ | 2.0 | 0.0 | 32.1 | 4.9 | _ | 5.8 |
| GAA last image (mm2) | 0.3 | 17.5 | 7.4 | _ | 6.1 | 6.0 | 12.1 | 8.4 | _ | 2.7 | 1.2 | 47.4 | 7.4 | _ | 7.9 |
| GAA PR (mm2/month) | 0.00 | 0.40 | 0.10 | 0.05 | 0.12 | 0.12 | 0.13 | 0.13 | 0.13 | 0.003 | 0.02 | 0.44 | 0.11 | 0.08 | 0.09 |

Table 2: Geographic atrophy area at the first image, at the last image, and progression rate per month. Median is shown for GAA PR because of its non-normal distribution. Med: median, stDv: standard deviation, GAA: geographic atrophy area, PR: progression rate.*The differences in progression rates between the three groups were not statistically significant.

| Table 3 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Eyes submited to surgery During the Study (4 patients)** | | | | | | | |
| | Before Surgery | | | | After Surgery | | | |
| | **Min** | **Max** | **Mean** | **stDv** | **Min** | **Max** | **Mean** | **stDv** |
| GAA PR (mm2/month) | -0.07 | 0.19 | 0.09 | 0.12 | 0.03 | 0.17 | 0.08 | 0.06 |
| SF CT PR (µm/month) | -3.9 | -6 | -0.4 | 2.4 | -1.1 | 20 | 4.7 | 10.2 |

Table 3: Geographic atrophy area progression rate and subfoveal choroidal thickness progression rate, before and after surgery. stDv: standard deviation, GAA PR: geographic atrophy area progression rate, SF CT PR: subfoveal choroidal thickness progression rate.

**Anexos**

1. Normas de publicação da revista Acta Ophthalmologica

2. Parecer da Comissão de Ética para a Saúde do Centro Hospitalar São João

**ORIGINAL PAPERS**

**Arrangement of the manuscript:** The manuscript should include the following: 1) title page; 2) abstract, and key words; 3) main text (introduction, materials and methods, results, discussion); 4) acknowledgement; 5) references; 6) figure and figure legends; 7) tables; 8) illustrations and graphics. For more information on manuscript format, please refer to the following guidelines.

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**Exmo. Senhor**

**Presidente do Conselho de Administração do**

**Centro Hospitalar de S. João – EPE**

**Assunto:** Pedido de autorização para realização de estudo/projecto de investigação

**Nome do Investigador Principal**: Luis Miguel Xavier Alves de Castro Teixeira

**Título do projecto de investigação**: Espessura da coroide e progressão das lesões de atrofia geográfica da retina

Pretendendo realizar no(s) Serviço(s) de Oftalmologia do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 15 / 05 / 2013

O INVESTIGADOR/PROMOTOR

Luis Miguel Xavier Alves de Castro Teixeira

19/08/2013

SÃO JOÃO
HOSPITAL

## Comissão de Ética para a Saúde do HSJ

## Parecer

Projecto de investigação intitulado "Espessura da coroide e progressão das lesões de atrofia geográfica da retina".

Estudo que se propõe vir a ser desenvolvido no Serviço de Oftalmologia do Centro Hospitalar São João EPE tendo como investigador responsável o aluno do mestrado integrado em Medicina Miguel Teixeira, sob orientação do Dr. Manuel falcão, que servirá de elo de ligação.

Do ponto de vista científico, trata-se de um estudo transversal que visa: a) relacionar a progressão de lesões de atrofia geográfica da retina com a espessura da coróide subjacente; b) avaliar a influência da cirurgia de cataratas nas referidas lesões, e c) caracterizar a evolução das mesmas lesões, em doentes seguidos no Serviço de Oftlamologia do HSJ. Para o efeito serão selecionados doentes com diagnóstico de atrofia geográfica, em relação aos quais serão colhidos dados clínicos e demográficos e obtidas imagens de autofluorescência, realizadas em momentos diferentes, para avaliar a progressão das lesões e a progressão da espessura da coróide.

Não estão previstos quaisquer riscos ou benefícios para os doentes incluídos no estudo e não serão realizados questionários.

Está previsto o acesso à informação clínica dos doentes através do investigador.

Não está prevista a obtenção de consentimento informado que, face à natureza do estudo pode ser dispensado.

O estudo está autorizado pelo diretor do Serviço de Oftalmologia, Prof Falcão dos Reis.

O estudo não é financiado e não comtempla ressarcimento que não é aplicável.

Em face da análise do protocolo proponho a sua aprovação pela CES do CHSJ.

Porto, 17 de Setembro de 2013

relator

Prof. Manuel Pestana

## 7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☐
NÃO APLICÁVEL ☒

## 8. TERMO DE RESPONSABILIDADE

Eu, Luis Miguel Xavier Alves de Castro Teixeira, abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 15 / 05 / 2013

Luis Miguel Xavier Alves de Castro Teixeira

O Investigador Principal

*PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO*

emitido na reunião plenária da CES de 20 / Setembro / 2013

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

O Doutor Filipe A... Coordenador da Comissão de...