

# Fractal Dimension Analysis of Widefield Choroidal Vasculature as Predictor of Stage of Macular Degeneration

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**Purpose:** To evaluate the fractal dimension ( $D_f$ ) of the choroidal vasculature using widefield indocyanine green (ICG) angiography and correlate it with the stage of age-related macular degeneration (AMD).

**Methods:** Widefield ICG angiography performed on 38 eyes was retrospectively analyzed using the FraLac application within the National Institutes of Health ImageJ software to determine regional fractal dimensions in the macular field and widefield. These values were then associated with a diagnosis of no AMD, non-exudative AMD (subdivided into early/intermediate stage vs. advanced stage), or exudative AMD (subdivided into with or without geographic atrophy). The mean values were compared using Wilcoxon's test.

**Results:** Early/intermediate non-exudative AMD and exudative AMD without geographic atrophy were found to have statistically significantly lower  $D_f$  values compared to an absence of AMD when examining the macular field. Exudative AMD with geographic atrophy was found to have a statistically significant lower choroidal fractal dimension compared to no AMD when studied in the widefield.

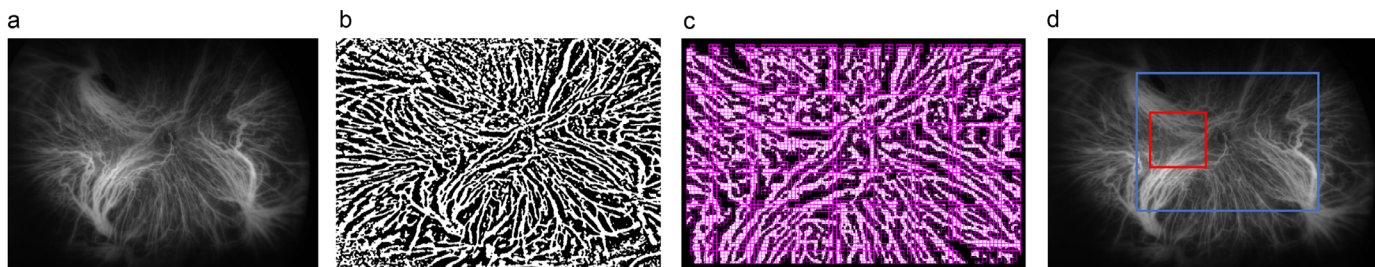
**Conclusions:** Advanced stages of macular degeneration were found to have significantly decreased the fractal dimensions of choroidal vasculature on widefield ICG compared to early/intermediate stages, possibly implying a generalized reduction in complexity and/or vessel caliber of the choroid with advancing stage of AMD. This finding agrees with previous understanding of the development of choriocapillaris atrophy in advanced macular degeneration.

**Translational Relevance:** These findings suggest that using automated fractal analysis techniques can aid in differentiating stages of macular degeneration and, with further study, may be used to predict advancement of macular degeneration.

## Introduction

Age-related macular degeneration (AMD) remains a leading cause of legal blindness in the world.<sup>1</sup> It is a disease affecting the outer retina, with close interdependence of the retinal pigment epithelium (RPE), photoreceptors, and choriocapillaris. A recent study has suggested that degeneration of the choriocapillaris may precede the changes in the photoreceptors that ultimately lead to vision loss.<sup>1</sup> As a result, further analysis of the morphologic changes in the choriocapillaris can help to better elucidate the pathophysiology of AMD.

Because the choriocapillaris is an arborizing vasculature structure, it can be analyzed as a fractal. First formalized by Benoit Mandelbrot in 1967, fractals are structures that are self-similar at various levels of magnification.<sup>2</sup> They are found throughout nature (e.g., snowflakes, coastlines) and within medicine (e.g., trabecular bone patterns, bronchiolar branching).<sup>3,4</sup> Fractal analysis of the retinal vasculature has been studied extensively with regard to disease processes such as diabetic retinopathy.<sup>5,6</sup> The advantage of fractal analysis is that it produces a quantifiable fractal dimension ( $D_f$ ) that can summarize the complexity or roughness of a structure, with higher values indicating higher complexity; that is, whereas a straight line would



**Figure 1.** (a) Representative ultra-widefield ICG angiography image taken with the Optos *California* ultra-widefield imaging device of the right eye of a 68-year-old woman with non-exudative macular degeneration in this study. (b) The same image after undergoing automated local binarization using the Niblack technique in ImageJ. (c) The previous image after one step of automated box counting to determine the fractal dimension using the FracLac application in the widefield; the box counting technique encompasses vessels with incrementally larger boxes and counts the number of boxes required. (d) The box in blue depicts the widefield analysis, and the box in red depicts the macular field analysis.

have a dimension of 1, a branching, self-similar tree can be understood as having a dimension fractionally higher than 1.<sup>2</sup>

Indocyanine green (ICG) angiography is an imaging technique that can image the choroidal vasculature because its cyanescent wavelength is able to penetrate the RPE. We hypothesize that atrophy from macular degeneration reduces the complexity and branching of the choriocapillaris, resulting in a decrease of its fractal dimension.<sup>1</sup> In this study, we investigated the fractal dimension of the choroid using ultra-widefield ICG angiography in patients with varying stages of AMD and controls.

## Methods

Ultra-widefield ICG was retrospectively reviewed in 38 eyes of 21 patients that were retrospectively collected as part of routine patient care at the Yale Eye Center from November 2016 to November 2017. Patients were categorized based on a diagnosis of AMD according to chart documentation from patient encounters at the time of image capture. They were classified as early or intermediate non-exudative stage AMD, advanced non-exudative stage AMD with geographic atrophy (GA), or exudative stage AMD with or without GA. Images were selected in the mid-venous phase and for minimal artifact. All images were obtained with a *California* ultra-widefield imaging device (Optos, Dunfermline, UK). This study complied with the tenets of the Declaration of Helsinki. This study was approved by the authors' institutional review board. Given its retrospective nature and the use of images only from routine patient care, the requirement for

informed consent was waived by the institutional review board.

Images were processed using ImageJ software (National Institutes of Health, Bethesda, MD, USA). The Niblack technique was used to binarize the images, which were then evaluated for fractal dimension using the box counting method over two regions: (1) widefield, centered at the optic disc from the temporal edge of the macula to an equivalent distance nasally, outside the superior and inferior arcade; and (2) macular field, from the temporal edge of the optic disc to the temporal edge of the macula, within the bounds of the superior and inferior temporal arcades (Fig. 1). The publicly available FracLac application was used (National Institutes of Health).<sup>7</sup>

Box counting relies on the equation  $N \propto \varepsilon^{D_f}$ , where  $N$  is the number of objects;  $\varepsilon$  is the linear scaling or magnification factor, which is equivalent to the inverse of the box linear dimension; and  $D_f$  is the fractal dimension.<sup>2</sup>  $D_f$  can then be calculated by creating a log-log plot of  $N$  and  $\varepsilon$  and solving for  $D_f$ , where  $D_f = \log(N)/\log(\varepsilon)$ .

Fractal dimensions were compared based on macular degeneration status (no AMD, non-exudative AMD, or exudative AMD) and by GA status (no AMD, AMD without GA, or AMD with GA) using Wilcoxon's nonparametric test for each pair (JMP 13 software; SAS Institute, Cary, NC).

## Results

The average fractal dimension of the widefield choroidal vasculature by ICG was 1.847, whereas the macular field fractal dimension was 1.772. The demographics are summarized in Table 1, and the

**Table 1.** Demographics of Study Population

Demographic	Value
Age (y), mean (range)	74.4 (24–90)
No AMD, n	11
Early/intermediate non-exudative AMD, n	11
Advanced non-exudative AMD, n	1 <sup>a</sup>
Exudative AMD without GA, n	7
Exudative AMD with GA, n	8

<sup>a</sup>Excluded from subgroup analysis.

**Table 2.** Summary of Means (95% CI) by Macular Degeneration Status

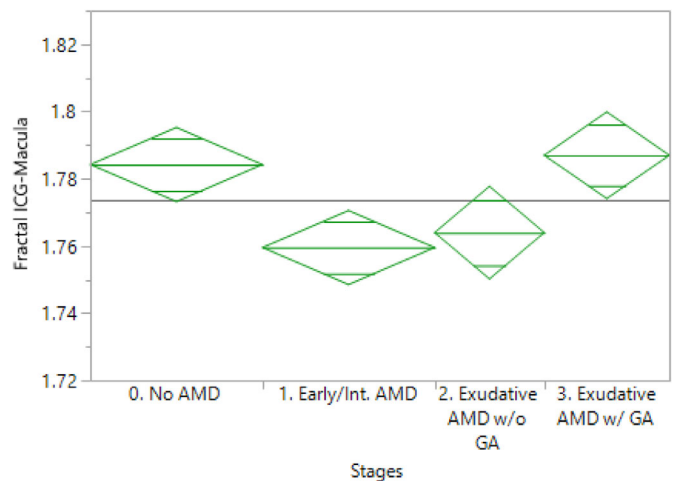
Status	ICG Fractal Dimension (95% CI)	
	Widefield	Macular Field
No AMD	1.856 (1.846–1.866)	1.784 (1.773–1.795)
Early/intermediate non-exudative AMD	1.847 (1.837–1.857)	1.760 (1.749–1.771)
Exudative AMD without GA	1.845 (1.832–1.858)	1.764 (1.750–1.778)
Exudative AMD with GA	1.837 (1.825–1.849)	1.787 (1.774–1.800)

subgroup analysis is summarized in [Table 2](#). Because only one eye in the study had advanced non-exudative AMD, it was excluded from the subgroup analysis.

In the widefield, only exudative AMD with geographic atrophy was found to have a statistically significant lower mean choroidal fractal dimension compared to no AMD ( $P < 0.05$ ), although both early/intermediate non-exudative AMD and exudative AMD without GA had lower mean choroidal fractal dimensions. These results are summarized in [Figure 2](#). In the macular field, eyes with early/intermediate non-exudative AMD or exudative AMD without GA were found to be statistically significantly different from eyes without AMD ( $P < 0.05$ ); however, neither the absence of AMD nor the presence of exudative AMD with GA was found to differ significantly. These results are summarized in [Figure 3](#).

## Discussion

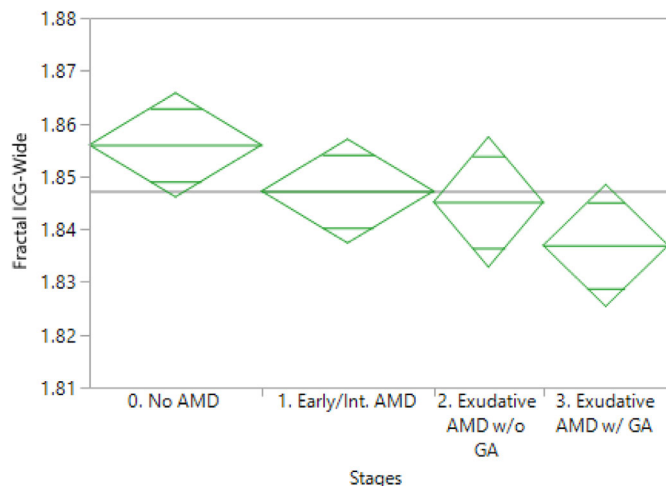
Although there have been numerous studies on the fractal dimension of retinal vasculature in ocular conditions such as diabetic retinopathy,<sup>5,6</sup> the literature on the fractal dimension in macular degeneration has been lacking. One abstract describes decreasing fractal dimension in progressive stages of macular degeneration based on color fundus photographs, although that study did not specifically examine the retinal or choroidal vasculature.<sup>8</sup> Because AMD is a condition



**Figure 2.** Plots of choroidal fractal dimensions scored for macula fields against macular degeneration status with confidence intervals. The top and bottom points of each diamond represent the 95% confidence intervals. The central horizontal line represents the group mean. The overlap marks above and below the mean line depict where group means can be considered to be statistically significantly different.

that affects the outer retina and choriocapillaris, the authors elected to analyze the choroidal vasculature for fractal dimension using ultra-widefield ICG angiography.

In the widefield, we found that exudative AMD with GA was correlated with a statistically significant decrease in fractal dimension. Non-exudative AMD without GA trended toward having a decreased



**Figure 3.** Plots of choroidal fractal dimension for widefields by ICG.

widefield fractal dimension but was not found to be statistically significantly different.

The fractal dimension can be approximated as a measure of the complexity of an arborizing network, although differences likely represent a decrease in complexity of arborizing networks, which may in turn reflect progressive choroidal dysfunction in progressive AMD. Thus, fractal dimension can provide an objective method with which to classify atrophy outside of choroidal thickness or vessel caliber.

Conversely, in the macular field, early/intermediate non-exudative AMD without GA and exudative AMD without GA were found to have fractal dimensions statistically significantly lower than when macular degeneration is absent, but neither of the cases that had exudative AMD with GA had fractal dimensions that were statistically significantly lower than those who carried no diagnosis of macular degeneration.

This result appears counterintuitive and conflicts with the findings of a decrease in fractal dimension in advanced AMD for the widefield. An explanation is that those with both exudative macular degeneration and GA have the most hypercyanescence from leakage or staining in the macula, which would artifactually elevate the fractal dimension. Although this artifactual effect may have been washed out in the widefield study, it is perhaps amplified in macular field studies, which were focused enough to reveal subtle differences in non-exudative, non-GA AMD that were only found to trend in the widefield study. Another possibility is that macular degeneration may have measurable effects on the peripheral choroid that have not been previously reported.

Recent studies have examined atrophy of the choriocapillaris using ocular coherence tomography, includ-

ing with angiography (OCTA).<sup>1</sup> A dye-based approach, as we report here, has several advantages over OCTA. First, OCTA relies on automated computation to segment vascular and cellular layers to identify the choroid. Devices have been shown to be inconsistent in segmenting the choroid, except in areas of absent RPE.<sup>9</sup> Second, OCTA at present is limited with regard to the detection of flow within individual choriocapillaris vessels, as well as within deeper choroidal vessels.<sup>1</sup> The long wavelength of ICG cyanescence penetrates the RPE to provide high-resolution imaging of the choroidal vasculature. Third, ICG allows for the use of ultra-widefield imaging techniques, whereas the use of OCTA, at present, remains confined to the macula. As found in this study, widefield studies may offer advantages over looking solely at the macula. The disadvantage of ICG is that it is dye based and is relatively contraindicated in patients with iodine allergy or significant liver disease or who are pregnant. Further, neither OCT nor OCTA was available for this study.

Limitations of this study include image artifact and lack of control for other possible contributing factors. Artifacts such as leakage or staining on the ICG would have increased the measured fractal dimension by increasing pixel density. Additionally, each image is not necessarily at the same photographic standard of centration and magnification; however, images were selected to have few, if any, significant areas of hyper- or hypocyanescence. Further, fractal analysis is relatively scale independent, minimizing the issue of variance in degree of magnification between pictures. That said, given the discrepancy of results in the widefield and macula field and the occurrence of dye-based artifacts, especially in most advanced stages of AMD, ultra-widefield angiography may not be optimal for analyzing the macula for fractal dimension. Finally, given the relatively small sample size of eyes, patients were not controlled for other conditions, such as systemic vascular disease. Further study in variations based on systemic vascular disease may further refine this model.

In summary, we observed that the stage of macular degeneration correlated with fractal dimension depending on widefield versus macular field analysis. This technique may be used in the future to aid in differentiating patients whose diagnosis of macular degeneration is in question and to aid in future subgroup analyses for other factors that may affect choroidal fractal dimension. This technique also provides a rapid, automated evaluation of choroidal vessels that is beyond a clinician's ability to rigorously observe in the clinic. Computer-aided techniques may help providers make clinical decisions based on an ever-growing array of data.

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