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Short communication

Age-related rarefaction in retinal vasculature is not linear

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ABSTRACT

The fractal dimension is a global measure of complexity and is useful for quantifying anatomical structures, including the retinal vascular network. A previous study found a linear declining trend with aging on the retinal vascular fractal dimension (D_F); however, it was limited to the older population (49 years and older). This study aimed to investigate the possible models of the fractal dimension changes from young to old subjects (10–73 years). A total of 215 right-eye retinal samples, including those of 119 (55%) women and 96 (45%) men, were selected. The retinal vessels were segmented using computer-assisted software, and non-vessel fragments were deleted. The fractal dimension was measured based on the log–log plot of the number of grids versus the size. The retinal vascular D_F was analyzed to determine changes with increasing age. Finally, the data were fitted to three polynomial models. All three models are statistically significant (Linear: $R^2 = 0.1270$, 213 d.f., $p < 0.001$, Quadratic: $R^2 = 0.1536$, 212 d.f., $p < 0.001$, Cubic: $R^2 = 0.1529$, 211 d.f., $p < 0.001$). The quadratic regression is significantly better than the linear regression ($p < 0.001$); however, the increase in R^2 from the quadratic model to the cubic model is not significant ($p = 0.97$). These results suggest that the decreasing trend of the fractal dimension associated with aging is better explained by the quadratic model than by the linear and cubic models in a sample with a broader age spectrum.

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The retinal vascular branching network is a complex structure because of its nonlinear branching pattern. It cannot be described using simple (i.e., Euclidean) geometric shapes such as lines or squares (Mainster, 1990). Previous studies have proven that the blood vasculature network of the human retina is a fractal (Family et al., 1989). The fractal dimension (D_F) of the retinal vasculature is a novel means of measuring the complexity of the retinal vessel branching network (Liew et al., 2008b).

D_F quantifies the degree of complexity into a single value and is particularly useful for describing features of physiological complexity (Goldberger et al., 2002) and non-Euclidean geometric shapes such as vascular networks (Masters, 2004). Fractal analysis is able to characterize the shapes of cellular organelles, cells, tissues and organs (Losa, 2005). These shape descriptors have been demonstrated to have sufficient sensitivity and specificity in diagnostic tests to discriminate the pathological state from the normal state (Kawasaki et al., 2011). Retinal vessels are good candidates for fractal analysis, as they develop predominantly on a surface of the retina, which can be regarded as two-dimensional. They are relatively easy to access with non-invasive methods, and they undergo structural changes in different conditions (Doubal et al., 2010).

The greater the value of the fractal dimension is, the higher the complexity of the structure will be (Lipsitz and Goldberger, 1992), and such an increase may indicate microvascular proliferation (Liew et al., 2008b). In contrast, the lower the value of fractal dimension is, the less complex and less dense the blood vessels branching network will be. The lower fractal dimension indicates rarefaction or loss of blood vessels. A previous study on the loss of complexity and aging hypothesized that physiologic aging is characterized by the loss of complexity in organ system function (Lipsitz and Goldberger, 1992). Any pathology that alters the retinal vasculature structure would change the distribution of the vasculature, thus resulting in a different fractal dimension value from that of normal. A previously study (Cheung et al., 2009) found that those with diabetic retinopathy have an increasing retinal vascular fractal dimension.

Previous studies have reported that the mean fractal dimension of normal human retinal vessels is 1.700 ± 0.016 (Family et al., 1989), 1.708 ± 0.073 (Daxer, 1993), 1.408 ± 0.025 (Macgillivray

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et al., 2007), 1.437 ± 0.025 (Liew et al., 2008b), 1.630 ± 0.06 (Traversi et al., 2008), 1.444 ± 0.023 (Li et al., 2010) and 1.506 ± 0.03 (Azemin et al., 2012). The discrepancies are possibly the result of the different protocols used such as variation in image resolution, different cropping regions (macula- versus disk-centered), methods used in image acquisition (color versus fluorescein angiogram), segmentation techniques and methods used to calculate the fractal dimension.

In the literature on aging, Liew et al. (2008a,b) noted that the fractal dimension of the retinal vasculature was inversely correlated with increasing age range from 49 to 97 years old and systolic blood pressure. This view is supported by another study on age-related rarefaction in the fractal dimension of retinal vessels where it was proven that the fractal dimension is linearly decreased with increasing age, regardless of whether the data from the right or left eye were used (Azemin et al., 2012). The researchers also reported the estimation of an average linear reduction in fractal dimension of 0.01 associated with each decade increase in age. However, both of the studies did not include any younger subjects.

A study conducted on a broader age spectrum (14–73 years old) was limited to only a small sample size ($N = 23$) because of the constraint of using a hand-tracing method to obtain the vessel segmentation (Landini et al., 1993). The work, however, did not find any correlation between the fractal dimension of the retinal vessel network and age. This research aims to overcome the limitations of previous works by increasing the sample size and broadening the age spectrum.

To assess the possible mathematical models of fractal dimension in aging, 852 retina images were collected from those who attended the International Islamic University Malaysia (IIUM) Optometry Clinic at various time points from January 2009 until June 2012 and presented for a general eye examination. Informed consent was obtained from the subjects or parents/guardians and approval from the local ethics Committee was granted in accordance with the principles laid down by the Declaration of Helsinki. The 45-degree field of view photographs were captured using a non-mydriatic Auto Fundus Nidek Camera AFC-230/210. Right eye retina images were used in this study, as a previous study reported that there is a similar linear decline of fractal dimension with increasing age regardless of whether the data are from the right or left eye (Azemin et al., 2012). This 45-degree field of view covers approximately the midway of the macula and optic disc as a center of the fundus photography. Fig. 1A illustrates the retina image used in this study. The cropping region was selected based on the number of images available with consistent cropping regions. The patient's medical records containing their respective retinal images were explored to extract the patient's data. There were 305 patients with missing data, which made the total available sample size 547. The inclusion criteria were as follows:

i. No lens opacity (cases of cataract were excluded). According to a study conducted by Li et al. (2010), there is a significant reduction of fractal dimension with lens opacity.
ii. No history of systemic disease that may affect retinal blood vasculature structure, such as diabetic retinopathy and hypertensive retinopathy (Cheung et al., 2009; Liew et al., 2008b)
iii. No significant underlying ocular pathology
iv. No high myopia (>6.00 D). The refraction data were obtained by reviewing the selected sample documents readily available in the IIUM Optometry Clinic. A study conducted by Li et al. (2010) found decreases in fractal dimension value in a high myopia group.

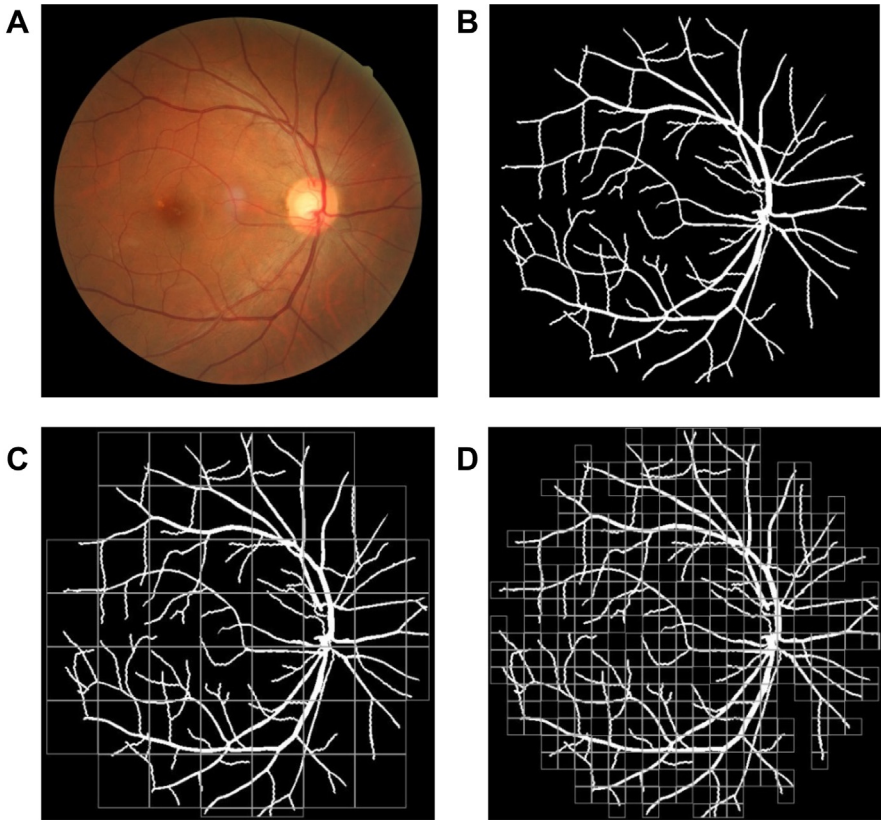

Fig. 1. Sample of the right-eye retina image of a 48-year-old male. (A) Color fundus camera. (B) Vessel segmentation. (C) Box-counting procedure with large-scale grid. (D) Bx-counting procedure with small-scale grid. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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