BRAZILIAN JOURNAL
OF MEDICAL AND BIOLOGICAL RESEARCH
www.bjournal.com.br

ISSN 0100-879X
Volume 42 (10) 870-992 October 2009

BIOMEDICAL SCIENCES
AND
CLINICAL INVESTIGATION

Braz J Med Biol Res, October 2009, Volume 42(10) 930-934

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The Brazilian Journal of Medical and Biological Research is partially financed by

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico
Ministério da Ciência e Tecnologia
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Ministério da Educação
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Brazilian Journal of Medical and Biological Research (2009) 42: 930-934
ISSN 0100-879X

Can the fractal dimension be applied for the early diagnosis of non-proliferative diabetic retinopathy?

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Abstract

The fractal dimension has been employed as a useful parameter in the diagnosis of retinal disease. Avakian et al. (*Curr Eye Res* 2002; 24: 274-280), comparing the vascular pattern of normal patients with mild to moderate non-proliferative diabetic retinopathy (NPDR), found a significant difference between them only in the macular region. This significant difference in the box-counting fractal dimension of the macular region between normal and mild NPDR patients has been proposed as a method of precocious diagnosis of NPDR. The aim of the present study was to determine if fractal dimensions can really be used as a parameter for the early diagnosis of NPDR. Box-counting and information fractal dimensions were used to parameterize the vascular pattern of the human retina. The two methods were applied to the whole retina and to nine anatomical regions of the retina in 5 individuals with mild NPDR and in 28 diabetic but opthalmically normal individuals (controls), with age between 31 and 86 years. All images of retina were obtained from the Digital Retinal Images for Vessel Extraction (DRIVE) database. The results showed that the fractal dimension parameter was not sensitive enough to be of use for an early diagnosis of NPDR.

Key words: Box-counting; Fractal dimension; Information fractal dimension; Retina; Vascularization; Non-proliferative diabetic retinopathy

Introduction

The retina captures and propagates images to the brain through receptor (cones and rods) and neural cells. Because of the high demand for oxygen due to elevated cellular activity, this tissue is highly vascularized, with a consequent complex vessel distribution (1-3). Therefore, a geometric description of this retinal vascularization is of great interest for the early diagnosis of some diseases that attack the vessels of the retina (4-6).

Complex geometric patterns similar to those formed by the retinal vessels can be described by fractal geometry. Fractal objects or processes have been described by Mandelbrot (7) and are characterized by the following properties: 1) self-similarity, which means that parts of an object or process resemble the whole object or process; 2) scaling, which means that the measured properties depend on the scale at which they are measured; 3) fractal dimension, which provides a quantitative description of self-similarity and scaling, and 4) the anomalous statistical properties of the fractals. From a practical point of view, the fractal dimension of a pattern describes how thoroughly the pattern fills the space in which it is embedded. For example, squares can completely cover a two-dimensional space and their fractal dimension is two. Retinal vessels span the two-dimensional space less completely, and their fractal dimension is less than two, but greater than one (8,9).

The fractal dimension has been employed as a useful parameter in the diagnosis of retinal diseases (10-15). Daxer (16) found a correlation fractal dimension for vascular pattern

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A.C.B. Kunicki was the recipient of a PIBIC/CNPq fellowship.
Received November 21, 2008. Accepted July 31, 2009. Available online September 4, 2009.

equal to 1.85 ± 0.06 (mean ± SD) in patients with proliferative diabetic retinopathy. This fractal dimension is significantly different from that found in normal individuals, in which this value is about 1.70 (17). Avakian et al. (13), comparing the vascular pattern of normal and mild to moderate non-proliferative diabetic retinopathy (NPDR) individuals, using box-counting (Df) and grid intersection (ρv) methods, found a significant difference between them only in the macular region. Significant differences in the fractal dimension of the vascular pattern were not observed for other retinal regions or for the whole retina. This significant difference in the box-counting fractal dimension of the macular region between normal and mild NPDR individuals can be used for an early diagnosis of NPDR. The possibility for the ophthalmologist to establish a parameter permitting the diagnosis of NPDR in the early phase is an important clinical goal.

The main objective of the present study was to answer the following question: is the fractal dimension a sufficiently sensitive parameter to be used for an early diagnosis of NPDR? A strategy developed in the present study to answer this question was to use a large sample for the control condition (28 diabetic but ophthalmically normal individuals) in order to reach consistent statistical conclusions.

Material and Methods

Computational method

We used 28 retinographies of diabetic, but ophthalmically normal patients (Figure 1A) and 5 retinographies (Figure 1D) of patients diagnosed with mild NPDR as shown elsewhere (18). All retinographies were obtained from the Digital Retinal Images for Vessel Extraction (DRIVE) database (18). The images were acquired from patients aged 31 to 86 years using a Canon CR5 non-mydriatic 3CCD camera with a 45-degree field of view. Each image has a size of 768 x 584 pixels, 8 bits per color channel and a field of view of approximately 540 pixels in diameter. The images were saved in JPEG-format (19).

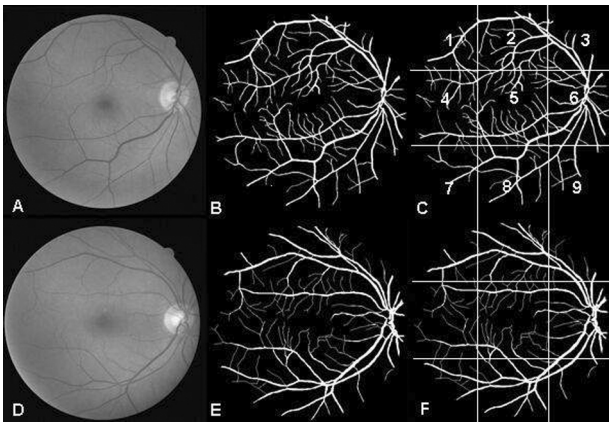

Figure 1. Retinography of normal (A) and mild non-proliferative diabetic retinopathy (NPDR) patients (D). The segmented image of control patients (B) and of patients with NPDR (E) was divided into nine anatomical regions (C,F): nasal superior (1), superior (2), superotemporal (3), optic disc (4), macular (5), temporal (6), nasal inferior (7), inferior (8), and inferotemporal (9). *Panels B*, *C*, *E*, and *F* are images with black fundus and white vessels, in which it is not possible to differentiate the control from the mild NPDR images with the naked eye.

Manually segmented images available in DRIVE were used for the calculation of the fractal dimensions (Figure 1B,E). The segmentation consists of extracting geometric information about the retinal vessels from the eye fundus images. The segmented images were saved in BMP-format. Figure 1 (panels B, C, E, and F) shows images of the segmentation of the retina with black fundus and white vessels, which do not permit the differentiation between control and mild NPDR images with the naked eye. Each image was divided into nine equal regions using the program Adobe Image Ready 7.0.1 (Figure 1C,F) and saved in BMP-format. After this procedure, box-counting and information fractal dimensions were automatically calculated for each retinal anatomical region and for the whole retina of control and NPDR individuals using the 1.3 Benoit™ Fractal Analysis System (TruSoft, USA) software.

Theoretical method (fractal dimension)

Box-counting fractal dimension. Box-counting is probably the method most frequently used to calculate fractal dimension. The procedure consists of covering the fractal object with N(r) boxes of different sizes, which contain at least one point of the fractal object. The Benoit™ software, depending on the size of the image, defines the side-length largest box and a coefficient of box size decrease that permit the determination of the size of the other boxes. Here, the side-length largest box was 146 pixels, the coefficient of box size decrease was 1.3 and the number of box sizes was 19. A plot of log N(r) versus log r (sides of the boxes) was then constructed. The slope of the line relating these two variables, with the inverted signal, is the dimension of box-counting that can be defined by the following equation (20):

$$D_{BC} = \lim_{\varepsilon \to 0} \left[\frac{\log N(r+\varepsilon) - \log N(r)}{\log(r+\varepsilon) - \log(r)} \right] \quad [1]$$

The above equation is the derivative of log N in relation to log r (d log N/d log r) that represents the slope of the plot log N versus log r. It is easy to show that if the base of the logarithm is changed from Neperian to decimal the D_{BC} value does not change. The sizes of the sides of the boxes were chosen by the Benoit™ software in a way that permitted us to obtain a graph of log N versus log r with a sufficient number of points to determine its slope with precision (or d log N/d log r). Nineteen different box sizes were determined

for an image of 768 *x* 584 pixels. The program permits to increase the number of boxes, but the fractal dimension remains the same when the box sizes are changed.

Information fractal dimension

The information dimension is defined by the following equation:

$$D_{INF} = \lim_{\varepsilon \to 0} \left[\frac{(S(r+\varepsilon) - S(r))}{\log(r+\varepsilon) - \log r} \right] \quad [2]$$

where

$$S(r) = -\lim_{N \to \infty} \sum_{i=1}^{N(d)} m_i \log(m_i) \quad [3]$$

is called Kolmogorov entropy, N is the number of boxes and $m_i = M_i / M$, where M_i is the number of points in the i^{th} box and M is the total number of points of the fractal object. The information dimension attributes weights to the boxes and those that contain a larger number of points weigh more than boxes with fewer points. The information dimension is calculated from the slope of the graph of the Kolmogorov entropy line and the logarithms of the sides of the boxes used to cover the fractal object (21). Similar to the box-counting, the value of the information fractal dimension is independent of the base of the logarithm used.

Statistical analysis

We first determined if the values of fractal dimensions of control and NPDR conditions from box-counting and information methods followed normal (Gaussian) distributions, in order to decide if parametric or nonparametric statistical analysis should be applied.

The Shapiro-Wilks test was used to test the normality of the distributions of the box-counting and information fractal dimension values of the vessel patterns in control and NPDR individuals. Data showing normal distribution were analyzed by a parametric test (*t*- or Z-test) and data showing non-normal distribution were analyzed by the nonparametric Mann-Whitney U-test to compare the average values of the fractal dimensions. The Z-test was applied to determine if the average value of fractal dimensions of the individuals with NPDR belongs to control Gaussian distribution.

Results

Tables 1 and 2 show measurements of position and variability for the box-counting and information fractal dimension values for nine retinal anatomical regions and for the whole retina of 28 diabetic but ophthalmically normal individuals (controls) and of 5 patients with NPDR. Table 1 shows that the box-counting fractal dimensions of the retinal vascularization pattern of diabetic but ophthalmically normal individuals (controls) followed a Gaussian distribution in all retinal anatomical regions as well as in the whole retina, except for the optic disc and temporal regions. The information dimension of the vascular pattern for the optic disc, temporal, inferotemporal, and inferior regions did not follow a normal distribution, but for other retinal regions and for the whole retina the distributions were Gaussians (Table 1). Table 1 also shows that the mean values of the box-counting and information fractal dimensions of the control were significantly different for each region of the retina as well as for the whole retina.

The box-counting fractal dimensions of vessel pat-

Table 1. Box-counting (D_{BC}) and information (D_{INF}) methods for determining the fractal dimensions of each anatomical retinal region and of the whole retina of 28 control individuals (without non-proliferative diabetic retinopathy).

Anatomical region	D_{BC}	$P_{Shapiro\text{-}Wilks}$ D_{BC}	D_{INF}	$P_{Shapiro\text{-}Wilks}$ D_{INF}	$P(D_{BC} = D_{INF})$
Nasal superior	1.299 ± 0.082	0.520	1.358 ± 0.092	0.210	0.014
Superior	1.359 ± 0.033	0.787	1.416 ± 0.037	0.385	0.000
Superotemporal	1.298 ± 0.067	0.660	1.339 ± 0.074	0.115	0.034
Optic disc	1.266 ± 0.122	0.001	1.314 ± 0.134	0.000	0.047*
Macular	1.212 ± 0.053	0.154	1.299 ± 0.036	0.537	0.000
Temporal	1.374 ± 0.133	0.000	1.436 ± 0.149	0.000	0.001*
Nasal inferior	1.265 ± 0.066	0.953	1.305 ± 0.079	0.598	0.046
Inferior	1.359 ± 0.043	0.147	1.411 ± 0.047	0.007	0.000*
Inferotemporal	1.348 ± 0.063	0.069	1.385 ± 0.067	0.030	0.024*
Whole retina	1.470 ± 0.025	0.728	1.516 ± 0.022	0.991	0.000

Data are reported as means ± SD. The Shapiro-Wilks test indicates the probability ($P_{Shapiro\text{-}Wilks}$) of the distribution of box-counting and information fractal dimensions to be Gaussian curves. The last column shows the probabilities of the average values of box-counting and information fractal dimensions to be equal, $P(D_{BC} = D_{INF})$. The *t*-test (for parametric distributions) and the Mann-Whitney U-test (for nonparametric distributions*) were used.

Table 2. Box-counting (D_{BC}) and information (D_{INF}) methods for determining the fractal dimension of each anatomical retinal region and of the whole retina of 5 patients with non-proliferative diabetic retinopathy (NPDR).

Anatomical region	D_{BC}	D_{INF}	$P(D_{BC})$	$P(D_{INF})$
Nasal superior	1.296 ± 0.147	1.343 ± 0.151	0.514	0.565
Superior	1.369 ± 0.026	1.412 ± 0.035	0.390	0.536
Superotemporal	1.312 ± 0.085	1.345 ± 0.086	0.419	0.472
Optic disc	1.306 ± 0.167	1.361 ± 0.190	0.687*	0.580*
Macular	1.239 ± 0.028	1.288 ± 0.023	0.305	0.616
Temporal	1.319 ± 0.180	1.385 ± 0.200	0.393*	0.580*
Nasal inferior	1.294 ± 0.071	1.341 ± 0.085	0.329	0.322
Inferior	1.353 ± 0.032	1.400 ± 0.042	0.556	0.269*
Inferotemporal	1.339 ± 0.086	1.404 ± 0.097	0.557	0.421*
Whole retina	1.462 ± 0.021	1.514 ± 0.026	0.617	0.519

Data are reported as means ± SD. $P(D_{BC})$ is the probability of the average values of the box-counting fractal dimensions of control and NPDR patients to be equal. $P(D_{INF})$ is the probability of the average values of the information fractal dimension of control and NPDR patients to be equal. The Z-test (for parametric distributions) and the Mann-Whitney U-test (for nonparametric distributions*) were used.

terns of controls and of patients with NPDR did not differ significantly regarding different anatomical regions of the retina or the whole retina (Table 2). The probability (P) of the normal and NPDR retinal fractal dimensions to be equal was 0.305 in the less probable case and it occurred in the macular region (Table 2). The information fractal dimension of vessel patterns of control and NPDR individuals did not differ significantly. In this case, the probability of the control and NPDR retinal fractal dimensions to be equal was in the least favorable case equal to 0.322, occurring in the inferior nasal region. A Z-distribution was used to determine these probabilities (Table 2).

For the box-counting fractal dimension in the optic disc (P = 0.687) and temporal (P = 0.393) regions and information fractal dimension in the optic disc (P = 0.580), temporal (P = 0.580), inferotemporal (P = 0.421), and inferior (P = 0.269) regions in which the fractal dimension values did not follow Gaussian distributions, the nonparametric Mann-Whitney U-test was used to determine this probability (Table 2).

These results show that the box-counting and information fractal dimensions are not adequate parameters to be used in order to distinguish between control and mild NPDR patients.

Discussion

A geometric description of the retinal vascular pattern has been proposed to facilitate the diagnosis of retinal vascular diseases. Avakian et al. (13) compared the vascular pattern of ophthalmically normal and mild to moderate NPDR using the box-counting and grid intersection methods and observed a significant difference between normal and NPDR only for the macular region. For the whole retina, no difference was observed in the fractal dimension of the vascular pattern between normal and NPDR patients.

The first point of the present study was to answer the question: can fractal dimension be safely applied for an early diagnosis of mild NPDR? To answer the question, we compared the retinal vascular fractal patterns of the control and mild NPDR using box-counting and information methods. The results did not show significant differences between control and mild NPDR vascular patterns. In the present study, the vascular patterns were compared using a quantitative method of region-based fractal analysis, as proposed by Avakian et al. (13), but no significant differences were observed between control and mild NPDR vascular retinal patterns. The difference between our results and those of Avakian et al. (13) may have been due to the larger number of control images in our investigation. This fact permitted the establishment of a vascular fractal pattern for the control. In addition, we also analyzed a larger number of regions than Avakian et al. (13). Daxer (10), using the correlation method, studied proliferative diabetic retinopathy in patients with neovascularization near the optic disc and found a fractal dimension with a mean value (± SD) equal to 1.85 ± 0.06. This value differs from that found by Family et al. (17) for normal retinal vascular patterns (D ≈ 1.7). Therefore, when applied to patients with advanced stages of vascular retinal diseases, fractal analysis seems to be sensitive enough to disclose a difference between normal and sick retinas. Supporting this conclusion, Cheung et al. (5), when examining the relationship between retinal fractal dimension and the different stages of retinopathy in young people with type one diabetes, concluded that an increasing retinal vascular fractal dimension was significantly associated with an increased stage of retinopathy.

Another objective of the present study was to analyze the relevance of the method used for the identification of the retinal vascular pattern. Different methods have been used for the calculation of the fractal dimension (17,22-26). Family et al. (17) calculated the fractal dimension (D) of the vascular pattern of the human retina using mass radius (D = 1.71 ± 0.07) and correlation (D = 1.72 ± 0.03) methods, but did not observe a significant difference between them. Previous studies from our group have shown that the fractal dimension values depend on the method used for the calculation of the fractal structure (27,28). In the present study, we showed that box-counting and information fractal dimensions differ significantly in each region as well as in the whole retina. These results suggest that the human retinal vessel pattern is a multifractal process, as pointed

out by Stosic and Stosic (29).

Our study showed that the fractal dimension was not a useful tool to distinguish between normal and mild NDPR, and reinforced our previous results showing that different values of fractal dimensions can be obtained depending on the method used to calculate the vascular retinal pattern.

Acknowledgments

We acknowledge Dr. Wamberto A. Varanda (Faculdade de Medicina de Ribeirão Preto, USP, Ribeirão Preto, SP, Brazil) for review, comments and suggestions.

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