

Fractal evaluation in retinographies of individuals with different grades of diabetic retinopathy

Avaliação fractal de retinografias de indivíduos com diferentes graus de retinopatia diabética

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ABSTRACT

Purpose: To evaluate the retinal blood vascular network of the retinographies of patients with different grades of diabetic retinopathy.

Methods: Ninety Retinographies (MESSIDOR database) were used, with different grades of diabetic retinopathy divided into 4 groups: no retinopathy (n=23), grade one (n=20), grade two (n=20) and grade three (n=27) diabetic retinopathy. The grades of diabetic retinopathy were classified according to the number of microaneurysms, number of hemorrhages and the presence of neovascularization. The images were skeletonized and quantified by fractal methods: dimension of box-counting (D_{bc}) and information (D_{inf}).

Results: The means of D_{bc} values of groups were around 1.25, without statistically significant difference in the dimension values between groups for whole retina. There was also no statistical difference in D_{inf} values between groups, whose means ranged between 1.294 ± 0.013 (group of grade 1) and 1.3 ± 0.017 (group of grade 3). The retinographies were divided into regions of equal areas. The fractal values of some retinal regions showed statistical differences, but these differences were not enough to show the sensitivity of fractal methods in identifying diabetic retinopathy.

Conclusion: The fractal methods were not able to identify the different grades of diabetic retinopathy in retinographies.

RESUMO

Objetivo: Avaliar a rede vascular sanguínea da retina a partir de retinografias de pacientes com diferentes graus de retinopatia diabética.

Métodos: Foram utilizadas 90 retinografias (banco de dados MESSIDOR), com diferentes graus de retinopatia diabética divididas em quatro grupos: sem retinopatia (n=23), retinopatia diabética de grau um (n=20), grau dois (n=20) e grau três (n=27). Os graus de retinopatia foram classificados conforme o número de microaneurismas, número de hemorragias e presença de neovascularização. As imagens foram esqueletizadas e quantificadas pelos métodos fractais: dimensão da contagem de caixas e informação.

Resultados: As médias dos valores das dimensões de contagem de caixas para todos os grupos foram próximas a 1,25, sem diferença estatisticamente significativa nos valores das dimensões entre os grupos para retina inteira. Também não houve diferença estatística nos valores da dimensão de informação entre os grupos, cujas médias variaram entre 1,294 ± 0,013 (grupo do grau 1) e 1,3 ± 0,017 (grupo do grau 3). As imagens retinianas foram divididas em regiões de áreas iguais. Os valores fractais de algumas regiões retinianas mostraram diferenças estatísticas, mas estas não foram suficientes para mostrar a sensibilidade dos métodos fractais na identificação da retinopatia diabética.

Conclusão: Os métodos fractais não foram capazes de identificar os diferentes graus de retinopatia diabética em retinografias.

INTRODUCTION

The number of children, teenagers and adults with diabetes has increased in recent years, and speculation for future years is alarming.^(1,2) More than 640 million people are predicted to have diabetes in the world 2040,⁽³⁾ showing that this disease is a serious public health issue.⁽⁴⁾

Diabetes mellitus is a metabolic disorder of multiple etiology characterized by the individual's chronic hyperglycemia, causing several organic complications.⁽⁵⁾ The plasma glycemic rate is high due to the low concentration or lack of insulin, or even a deficiency in the action of this hormone, promoting the non-uptake of glucose by cells.⁽⁶⁾ Thus, several tissues will be affected by this disorder, leading to macrovascular and microvascular complications. As a result, there will be functional impairment of various organs, such as vessels, heart, nerves, kidneys, and eyes.⁽⁶⁾

Individuals with diabetes may develop diabetic retinopathy because hyperglycemia promotes structural and functional changes in retinal capillaries.⁽⁷⁾ Among ophthalmopathies, it is one of the causes of visual impairment that can lead to blindness.⁽⁸⁾ The early stage of retinopathy is known as non-proliferative diabetic retinopathy (NPDR), which is a disease characterized by microaneurysms (Ma), hemorrhages (H), and capillary obstruction.^(7,9) Microvascular abnormalities, dilations, and venous loops develop because of increased areas of hypoxia. According to the number and type of lesions, NPDR can be classified as mild, moderate and severe. Patients usually do not have any visual problems, but the prognosis is not good due to the progress of the disease, in addition to being involved with diabetic macular edema.⁽¹⁰⁻¹²⁾

The proliferative phase can be characterized by neovascularization (Nv), increased ischemic regions, H in the vitreous, and retinal detachment may occur.^(7,13) Most people who have type I and II diabetes are at risk for developing retinal complications, increasing the likelihood over the years.^(7,12)

The retinal blood vascular network is considered to be a fractal structure, due to the process of vascular branching to present self-similarity at different scales.^(14,15) Thus, several works have used fractal geometry to assess the complexity of the retinal vascular network when affected by any disease. These studies may bring the possibility of applying fractal tools as a parameter for the degree of retinopathy or how much the dimension of the vascular network is altered.

This study aimed to evaluate the retinal blood vascular network from retinographies of the patients with different grades of diabetic retinopathy.

METHODS

Retinal images

Retinographies were obtained from the MESSIDOR database (<https://paperswithcode.com/dataset/messidor-1>), whose instructions allowed the formation of the groups evaluated according to the grade of retinopathy. Ninety retinal images (2,240x1,488 pixels resolution) were used, with different grades of diabetic retinopathy divided into four groups: no retinopathy (n=23), grade one (n=20), grade two (n=20), and grade three (n=27) diabetic retinopathy. The grades of diabetic retinopathy were classified according to the number of Ma, number of H, and the presence of Nv: grade one (with up to five regions with Ma, without the presence of H); grade two (between six and 14 regions with Ma or up to four regions with H); grade 3 (from 15 regions with Ma, or from five regions with H or presence of Nv). Grade 3 corresponds to the most advanced level of diabetic retinopathy and is the only one that fits, if any, the stage of Nv. Fundus images were acquired through three ophthalmology departments using a 3ccd video camera on a Topcon Trc-nw6 non-mydratic retinal camera (Topcon Corporation, Tokyo, Japan) with a 45° field of view.

Skeletonization of retinographies

The images of retinal vessels were manually skeletonized using Microsoft's Paint software (Microsoft Corporation, Redmond, Washington, United States), as shown in Figure 1. This skeletonization process allows for binarization (vessels in white and background image in black) and the uniformity of vessel thickness. The vessels were covered with a black trace of thickness around one pixel. Afterwards, the software performed a process in which the black trace was converted to white, while the rest of the image was transformed into black. Thus, the retinal vascular network image became binary and skeletonized, with vessels represented by single thickness lines in white and the background image in black. The fractal methods perform the calculation only on white pixels, therefore the vessels stayed in white. This method is based on the construction of an image (traces that cover retinal vascular network) superimposed on the preexistent image (retinography, which is the background image). After the image with traces superimposed of vessels (skeleton of vascular network) is finished, the background image is deleted, leaving only the skeleton of the vascular network. Using the PhotoScape v.3.7 software (Mooii Tech Co., Cheonan, South Chungcheong, Republic of Korea), each skeletonized image was divided into nine regions

of equal area: optic disc, inferior, macular, inferior nasal, superior nasal, superior, temporal, inferior temporal and superior temporal.

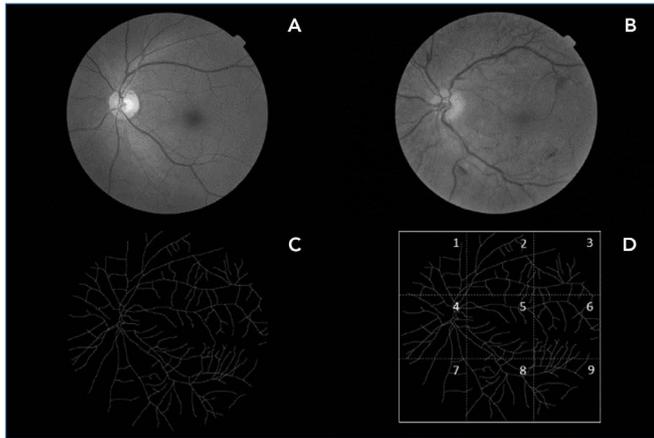


Figure 1. Retinal image of an individual without diabetic retinopathy (A). Image of an individual with grade 3 diabetic retinopathy (B). Skeletonized image of image A (C). Image C divided into regions (D): superior nasal (1), superior (2), superior temporal (3), optic disc (4), macular (5), temporal (6), inferior nasal (7), inferior (8), and inferior temporal (9)

Evaluating the dimension of the retinal vascular network by fractal geometry methods

The skeletonized images of the retinal blood vessel network were quantified by two fractal methods (dimension of box-counting and information) using the Benoit 1.3 Fractal Analysis System (Trusoft, St. Petersburg, FL, United States). To obtain the box-counting dimension (D_{bc}), the skeletonized image of the vascular network was covered by a certain number of boxes (N) with size r ($N(r)$). Boxes that contain at least one point of the fractal object are counted. The procedure was repeated with different sets of boxes containing, at each step, a greater number of boxes $N(r)$ as the boxes were reduced in size (r). The pixel counting process is represented by a double log graph of $N(r)$ as a function of the boxes with size r .⁽¹⁶⁾ The slope of this relationship with the inverted sign is the D_{bc} . To obtain D_{bc} value of the whole retinal image, we used 23 sets of boxes with different sizes, the side length of the largest box was 372 pixels, and the reduction coefficient of the box size was 1.3.

In the information dimension (D_{inf}), the skeletonized image of the vascular network was also covered by several boxes of varied sizes, however the counting was performed based on the probability of occupation of the boxes by the vascular network. The procedure was repeated as in the method of D_{bc} ; different sets of boxes containing, at each step, a greater number of boxes $N(r)$, as the box size

(r) was reduced. Subsequently, a double logarithm plot of the Kolmogorov entropy is plotted against the sides of the r boxes. The D_{inf} is obtained by the slope of the double logarithm plot of the Kolmogorov entropy ($S(r)$) versus r , with an inverted sign.⁽¹⁶⁾ $S(r)$ is defined as Equation 1.

$$S(r) = \lim_{N \rightarrow \infty} \sum_{i=1}^{N(r)} m_i \log(m_i) \quad \text{Equation 1}$$

where N is the number of boxes, $m_i = M_i/M$, M_i is the number of points in the i -th box and M is the total number of points of the vascular network and r is the size of the boxes. For the calculations of the D_{inf} we used nine sets of boxes with varied sizes, the side length of the largest box was 372 pixels, and the reduction coefficient of the box size was 2.0.

Statistical analysis

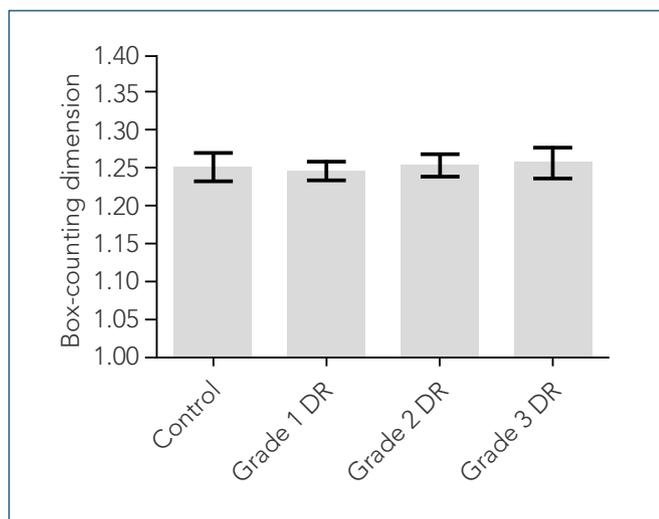
The Shapiro-Wilk test was used to assess the normality of the values of the fractal dimensions (D_{bc} and D_{inf}) for each group. Analysis of variance (Anova) test with Tukey's post-hoc test was used to assess groups whose fractal values followed a normal distribution. However, Kruskal-Wallis test with Dunn's post-hoc test was used for groups that did not follow normal distribution.

RESULTS

Figure 2 shows the mean with standard deviation of the fractal dimension values of the retinal vascular network for each group, since all data followed a normal distribution. The averages of fractal dimension values for all groups were close to 1.25 (1.25 ± 0.019 to control group; 1.25 ± 0.013 to grade 1 DR; 1.25 ± 0.015 to grade 2 DR; and 1.26 ± 0.021). There was no statistically significant difference between groups for whole retinal D_{bc} values ($p=0.13$).

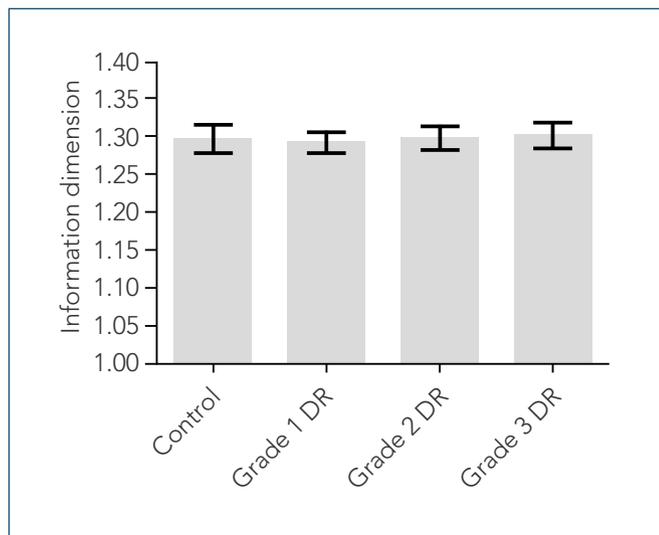
There was also no significant difference when comparing the D_{inf} values of the vascular networks displayed in the skeletonized images of each group ($p=0.12$). Since the data of some groups did not follow a normal distribution, Figure 3 shows the mean with standard deviation of the entire retinal D_{inf} values for each group. The means with standard deviations varied between 1.294 ± 0.013 (group of grade 1) and 1.3 ± 0.017 (group of grade 3). The means of control group and group of grade 2 were 1.298 ± 0.019 and 1.3 ± 0.016 , respectively.

When the analysis of D_{bc} values of the vascular networks of the regions of each retina was performed (optic disc, inferior, macular, inferior nasal, superior nasal, superior, temporal, inferior temporal and superior temporal), there were significant differences between the groups



DR: diabetic retinopathy

Figure 2. Representation of the means with standard deviations of the D_{bc} values of the groups with and without diabetic retinopathy (DR).



DR: diabetic retinopathy

Figure 3. Representation of the means with standard deviations of the D_{inf} values of the groups with and without diabetic retinopathy (DR).

($p < 0.05$) for some regions. Table 1 shows the means and standard deviations of the D_{bc} values of the vascular network of the retinal regions for each group.

Table 2 represents the analysis of the fractal values for the D_{inf} method of the vascular network of the different retinal regions.

Thus, we can observe that the differences found for the fractal methods of box-counting and information between groups were the same for certain regions. The control group was different from the group with grade 1 retinopathy and also grade 2 in the inferior region. The control group also showed a significant difference between grade 1 group in the inferior temporal region. In the inferior and superior nasal regions, there was a statistical difference between grade 1 and 3 groups.

The D_{bc} fractal values also showed difference between the control and the grade 1 group for the optic disc region, while the D_{inf} values did not show any difference.

DISCUSSION

Fractal is a tool that can measure several complex structures in nature, and they obviously have properties of self-similarity and scale dependence. Vascular network is regarded as a fractal structure; therefore, it can be evaluated by fractal methods.⁽¹⁵⁾ Some diseases can affect the vessels of some ocular structures such as cornea, choroid, and retina.⁽¹⁷⁻¹⁹⁾ Some patients with diabetes mellitus are likely to develop diabetic retinopathy, thus leading to retinal vascular disorders, such as angiogenesis because of alterations in vascular architecture. Some vascular alterations may promote differences in the degree of space filling by the vessels in the retina, which is possible to be measured by fractal methods.⁽²⁰⁾

The blood vascular network is a structure composed of bifurcations and therefore has a complex shape.^(14,15)

Table 1. Means with standard deviations of the D_{cc} values of the groups with and without retinopathy

	Optic disc	Inferior	Macular	Inferior nasal	Superior nasal	Superior	Temporal	Inferior temporal	Superior temporal
Control	0.855±0.04 ^a	0.823±0.03 ^{ab}	0.766±0.06	0.737±0.05	0.708±0.06	0.783±0.04	0.802±0.04	0.775±0.05 ^a	0.753±0.05
Grade 1	0.823±0.04 ^a	0.775±0.04 ^a	0.74±0.05	0.701±0.06 ^a	0.703±0.05 ^a	0.769±0.04	0.779±0.04	0.724±0.05 ^a	0.724±0.05
Grade 2	0.841±0.03	0.784±0.04 ^b	0.754±0.05	0.715±0.05	0.737±0.05	0.767±0.04	0.792±0.04	0.742±0.05	0.723±0.06
Grade 3	0.852±0.03	0.797±0.04	0.768±0.06	0.759±0.05 ^a	0.748±0.06 ^a	0.792±0.04	0.8±0.05	0.754±0.04	0.758±0.06

Letters repeated in the same column represent a statistical difference ($p < 0.05$) between groups for a given retinal region.

Table 2. Means with standard deviations of the dimension information values of the groups with and without retinopathy

	Optic disc	Inferior	Macular	Inferior nasal	Superior nasal	Superior	Temporal	Inferior temporal	Superior temporal
Controle	0.989±0.04	0.935±0.03 ^{ab}	0.871±0.06	0.837±0.06	0.809±0.06	0.89±0.04	0.902±0.04	0.881±0.07 ^a	0.848±0.06
Grade 1	0.963±0.05	0.883±0.04 ^a	0.843±0.06	0.788±0.08 ^a	0.801±0.06 ^a	0.876±0.05	0.873±0.04	0.824±0.06 ^a	0.826±0.07
Grade 2	0.985±0.04	0.889±0.05 ^b	0.859±0.05	0.81±0.07	0.849±0.06	0.88±0.04	0.897±0.05	0.842±0.05	0.823±0.06
Grade 3	0.996±0.03	0.91±0.05	0.869±0.06	0.862±0.06 ^a	0.854±0.07 ^a	0.898±0.04	0.909±0.06	0.858±0.06	0.861±0.06

Letters repeated in the same column represent a statistical difference ($p < 0.05$) between groups for a given retinal region.

Nevertheless, the self-similarity observed in different scales, main characteristic of fractal object, indicates not just the shape complexity of the analyzed object, but also brings the idea of occupied space by object. The fractal geometry is a quantifier of the morphologic complexity and space filled by object, which is revealed by a dimension. The higher or lower dimension value expresses greater or lesser complexity, respectively, within a certain range of scales. This aspect is important in diabetic retinopathy, as this disease is involved with small vessel disorders. Moreover, the increase or decrease of these fractal values also correspond respectively to a greater or lesser area of occupation of the fractal structure. The complexity and space filled by retinal vessels are also expressed by increase or decrease in the development of vascular network that is related to the branching and density of the vessels.⁽²¹⁾

Some studies performed by some authors⁽²²⁻²⁴⁾ applied fractal geometry to assess retinal vascular network disorders and they have validated the effectiveness of this tool. However, a study with segmented retinal images showed that fractal methods (dimension of box-counting and information) were not sensitive in the early diagnosis of NPDR.⁽²⁵⁾ Another study showed that multifractal geometry, fractal methods (dimension of box-counting and information), and lacunarity applied to skeletonized retinal images both complete and divided into regions were not able to identify NPDR.⁽²⁰⁾

The identification of vascular changes caused by diabetic retinopathy is highlighted by aneurism, H, Nv etc.^(26,27) The degree of retinopathy presented in this study is related to the presence and the number of these alterations. We would expect that at least the retinographies of patients with grade 3 retinopathy would show some increase in the fractal values because of angiogenesis, despite not being present in all images classified with grade 3. However, our results show fractal methods applied in retinographies were not able to identify significant changes on retinal vascular network in different grades of diabetic retinopathy. Even with these parameters, the scale was not enough to disclose any difference in the distribution of vessels from the skeletonized images. Although the data in Tables 1 and 2 presented some statistical differences for some retinal regions, this information does not qualify the methods as capable of identifying diabetic retinopathy.

Retinal images should exhibit good quality and pattern. This reflects on the segmentation of the image and, therefore, in obtaining the fractal dimension.⁽²⁸⁾ The procedures used for retinal images acquisition/processing and fractal dimension calculations must be

standardized.⁽²⁹⁾ This would help to know the real potential of fractal methods. The segmentation process consists of extracting the object of study within an image, in our case the retinal vascular network, resulting in a binary image in which the vessels are in white and the background image in black or opposite (vessels in black and background in white).^(30,31) Skeletonization, which is also a segmentation process, consists of obtaining binary retinal vessels, but vessel diameters are represented by a very thin line.^(16,30) These image processing methods are necessary when performing quantification by mathematical methods such as fractal geometry.^(28,30)

In our selection for image skeletonization, there were still images with changes in brightness. Retinal images may show differences in brightness, so darker areas are noticeable. These areas with less brightness have low sharpness for vessel identification, which can cause difficulty in both the automatic and manual segmentation processes. In addition, retinal hemorrhages present in the images, depending on the degree, sometimes reduce the visualization of the vessels and create obstacles in the segmentation process.⁽²⁸⁾

Some imaging techniques in ophthalmology have been widely used recently in the diagnosis of eye diseases, such as optical coherence tomography and fluorescein angiography.⁽³²⁾ These techniques produce images with good resolution that help to obtain a better-segmented image, as observed in the study conducted by Zahid et al.,⁽²³⁾ in which angiographic images of optical coherence tomography were used to obtain the fractal dimensions of the retinal vascular network. These procedures provide a better contrast image of the vessels with the background. This avoids the loss of visual information from the vascular network and allows that a segmented image is more faithful to the original image.

The main limitation of this study must be the non-evident capillary network. Since the capillary network is important for the evaluation of retinal ischemia and a pre-Nv finding in NPDR. In vascular network growth, recent blood vessels are smaller compared to preexisting vessels. Thus, Nv is a process that involves smaller vessels and capillaries,⁽⁷⁾ because, obviously, the smaller vessels are arising from larger vessels in the branching process. There is no good visualization on smaller vessels and capillaries in normal retinography. Therefore, this implicates the loss of information in the skeletonized images. Consequently, fractal methods in this condition were unable to accurately express the changes in the microcirculation in retinographic images.

CONCLUSION

The fractal methods (dimension of box-counting and information) were not able to identify changes in the vascular network displayed in the retinographies of patients with different grades of diabetic retinopathy. However, when the retinal images were divided into regions of equal areas, the fractal values of some retinal regions showed statistical differences. But these statistical differences were not enough to show the sensitivity of fractal methods in identifying diabetic retinopathy.

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