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Fractal Analysis of Retinal Vessels and the Relationship with Cerebral Microcirculation Pathology – A Narrative Review

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Abstract
One of the most reliable *in vivo* examination methods of human microvasculature is represented by ophthalmoscopy. Due to ophthalmoscopy, retinal circulation can reveal multiple morphological details that can serve as diagnosis biomarkers for retinal vessels diseases. Since retinal vessels are a component of carotid circulation that is designed to brain tissue, there are similarities between retina and brain circulation that can open the opportunity to an indirect assessment of the cerebral microcirculation by fundus examination. Fractal analysis of retinal microcirculation is one of the most exact methods that can offer mathematical details regarding the morphological characteristics of retinal circulation and, in the same time, regarding cerebral microcirculation. The aim of this paper was to describe the implication of fractal analysis of retinal circulation as diagnosis and prediction tools for cerebral ischemic diseases. The fractal analysis could represent a performant non-invasive method that can offer precise details regarding retinal circulation features that can be used as biomarkers in cerebral ischemic diseases.

Keywords: Retinal vessels; Fractal analysis; Cerebral microcirculation; Cerebral small vessel diseases; Cerebral ischemia

Introduction

Retinal vasculature assessment constitutes one of the most reliable methods to quantify the reflection of various general diseases on retinal vessels. Many important systemic diseases such as cardiovascular diseases [1], cerebrovascular diseases [2], diabetes mellitus [3], Alzheimer's disease [4], chronic kidney disease [5], hemoglobinopathies and associated hypoxia [6] had associated retinal vessels changes. Ophthalmologic diseases such as myopia, amblyopia, glaucoma or age related macular degeneration have been characterized using fractal analysis of retinal vessels, emphasizing the utility of this mathematical method in retinal microvasculature morphology assessment [7-10].

Despite the rapid assessment of retinal microvessels by fundus examination (either by direct or indirect ophthalmoscopy or by biomicroscopic fundus evaluation), the quantitative methods are more accurate, bringing more exact details about the quantification of vessels diameters and their relationship with the diseases previously mentioned [11]. A screening method for various pathologies reflected in the retinal vasculature is the examination of the fundus by an experimented ophthalmologist. However, objective methods such optical coherence tomography (OCT) or retinal photography with a fractal analysis of retinal vessels could bring more precise information of retinal vessels morphology associated with specific diseases [12,13]. Due to the transparency of ocular

tissues, retina observation is a convenient method for *in vivo* evaluation of the retinal circulatory system that presents a similar pattern with cerebral circulation. [13]

Analyzing the retinal microvasculature morphology by optical coherence tomography (OCT) or fractal dimensions (FD) (based on retinal photography) the normal histological structure of the retina, and the presence of pathological structures inside of retinal layers are visible and easy to be quantified [14]. Structural changes reflected in the pattern of retinal microvasculature aspects on OCT examination and FD can constitute valuable biomarkers useful for disease characterization, classification, prognostic, and prophylaxis. [15]. The retina is a layered tissue that are able to convert the light in action potentials that are transmitted to the cortex by neuronal synaptic transmissions, and this continuity of biological processes and their pathways from the environment to the brain, are conferring to the retina the quality of brain extension. Due to the transparency of ocular media, the examination of retina is accessible and constitutes an in vivo examination of human vessels, their aspects being possible to be extended to other vascular territories such as brain microvasculature. A specific pattern of retinal microvasculature was reported to be associated with cerebral small vessels diseases such as lacuna infarcts and leukoaraiosis [2].

The branching pattern of the retinal circulation in the living normal human retina is the subject of this review. This paper covers the following topics: the concepts of fractal analysis of retinal microvasculature, brain microcirculation features, the fractal dimensions of retinal vessels, and the relationship with cerebral vascular diseases. The paper presents a discussion of the optimal analysis of fractal dimension assessment for retinal microvasculature branching pattern and their importance in cerebral microcirculation and cerebral vascular diseases.

The Concepts of Fractal Analysis of Retinal Microvasculature

The histology of the retina consists in ten layers represented by: internal limiting membrane, nerve fibres layer (ganglion's cells axons that are specialized in visual signal transmission to geniculate cortex and further to visual cortex), ganglion cells layer (the body of ganglion cells), inner plexiform layer (bipolar cell's axons), inner nuclear layer (bipolar cell's bodies and horizontal cells), outer plexiform layer (horizontal cell's dendrites and inner segment of photoreceptor cells represented by cones and rods), outer nuclear layer (photoreceptor cell's bodies), external limiting membrane, pigment epithelium and Bruch's membrane [16]. The importance of retina structure examination is based on the location of different pathological processes inside of retinal layers. The location of the edema, layer disruptions, pathological accumulation of metabolic products, or vascular permeabilization is essential for the diagnosis and treatment of specific disorders, either reflecting systemic diseases or local retinal pathologies. Moreover, the assessment of structural changes of retina architecture could bring essential details for the prognosis of visual function [17].

In human retina, the circulation is supplied by the central retinal artery, and the main venous circulation is represented by the central retinal vein. Both systems of blood supply are visible to emerge from the optic disc (representing the optic head detectable by ophthalmoscopy), and their drawing on the retinal surface is assembling branching in superior and inferior field of the retina, dividing themselves into superior-temporal, superior-nasal, inferior-temporal and inferior-nasal branches [18]. They supply the inner layer (nerve fibres layer) and glial cells, which represent two-thirds of retinal thickness [19]. The exterior part of the retina is supplied by choroidal circulation. The retinal artery and retinal veins that are visible by fundus examination are not crossing themselves and at the periphery of the retinal are dividing into arterioles, venules, and capillaries, which are forming a very efficient network. There is an important area of the retina called macula, which contains an avascular structure specialized in central, high-resolution color vision. The macula has the following areas: foveola, foveal avascular zone, parafovea and perifovea [19]. Due to the absence of retinal vessels at this level of the retina, fractal analysis of this area is not possible; therefore, a different examination of the macula is useful. Taking in consideration that pathological processess of the macula can represent important elements in a precise diagnosis in various ocular pathologies (e.g., diabetic retinopathy, age related macular degeneration) by liquid accumulation or layers disruptions, the fractal analysis of retinal circulation has an important limitation in offering information related to

this retinal structure. Optical coherence tomography must complete fractal analysis of retinal vessels to obtain the best appreciations of retinal morphology, that are important for diagnosis [12].

The application of fractal geometry in retinal vessels structural analyses started from clinical concepts according with the fundus examination can bring details in retinal microvascular changes in systemic and ophthalmologic diseases. Severe alteration of retinal microvasculature is easy to be observed, but global assessment of topographic areas of the retina and their vasculature require more precise techniques. Fractal analysis can discriminate the pathological shapes from normal structures showing sensitivity and specificity as a diagnostic test by specifically retinal microvascular patterns associated with various disorders [20]. Fractal analysis is mostly referred to as a branching pattern building composing, a theoretical model of blood vessel structural features, offering information about blood flow according with vessel diameters, bifurcation angles, numbers, and branching lengths. Besides global assessments of these features of retinal circulation, the punctual pathological changes can also be characterized.

Fractals are structures that show similarities at different magnification. They can be assimilated as a form of symmetry at different dimensions regarding the changes of scale. There are several types of fractals. Regular fractals can be generated on a computer according to a precise algorithm [21]. The random fractals are the fractals found in nature and that have a similarity only over a finite magnification. Their density decreases with the distance from any fixed point on them [21]. Added to these, there are other fractals type called anisotropic fractals (mostly refer to surface fractals), where the changes of vertical or horizontal scales are leading to different images of the same surface according to the direction where the fractal analysis is applied (e.g. mountains silhouettes or other geographical shapes in nature) [20]. Laplacian fractals are another class of fractals defined based on Laplacian equation and are used to describe growing objects such as snowflakes, aggregating particles, or crystal growth [22].

Several computer models can mimic fractal growth. One of them is simulating the branching pattern of the retinal circulation of human retina more accurately than others. This example is referring to the diffusion-limited aggregation (DLA) method that simulates the branching patterns like arteries and veins branching in the human retina [20].

Brain Microcirculation Features

The vascular architecture of cerebral microcirculation plays an important role in several vascular diseases such as cerebral small vessels diseases such as lacuna infarcts and leukoaraiosis [2]. Added to vascular pathology, small cerebral vessels branching was also related to cognitive decline associated with Alzheimer's disease, suggesting that monitoring changes in the peripheral retina microcirculation can be useful in monitorization of the cognitive decline [4]. Moreover, the authors suggested that cerebral atrophy associated with Alzheimer's disease is correlated with arborization of cerebral microcirculation, which evolves to paucity of branching, proportional with cognitive decline progression.

Changes of cerebral circulation in the penetrating area arteries are important pathogenetic mechanisms associated with small cerebral vessels ischemic or haemorrhagic stroke. The best visualization of cerebral microcirculation can be achieved by cranial computed tomography angiography. By flow-diameter scaling law and mass conservative principle, there is a relationship between parent vessel diameter (D0) and small vessels diameter (D1 and D2), resulting by branching that related to the formula: $D0k = D1k + D2k$, where the k represents the branching exponent [23].

Arterial branching system is a candelabra-like drawing, less tortuous appearance than venous retinal circulation, and with different bifurcation, patterns compared with the venous system. The subsequent branches are positioned along with their paternal system, on a longer distance than in the venous system. Retinal veins are less numerous, and their entrances in the central vein are at the right entrance angle. Similarly, the cerebral circulation is characterized by the same pattern, adding the coiling phenomenon (the branches are coupled with parental arteries for a long distance, and after this trajectory, they are coiling around them). At the transition between white and gray matter, arteries are sinuous [24].

The Fractal Dimensions of Retinal Vessels and their Relationship with Cerebral Small Vessels Diseases

Cerebral small vessel disease (CSVD) represents about 25% of total cerebral ischemic disorders and is characterized by specific clinical symptoms and neuroimaging features [25]. Specific histopathologic changes characterize the CSVD (loos of smooth muscle cell in tunica media, degeneration of elastic lamina, proliferation of fibroblasts)[26]. Moreover, CSVD represents the first cause of neurologic disability and cognitive decline in the elderly [26]. Taking into account the importance of CSVD's, the understanding of pathophysiological mechanisms, and the development of diagnosis methods, together with the improvement of prophylaxis method and beneficial therapies, could reduce their impact on life quality and could increase the life expectancy [26].

One of the most important diseases that contribute to structural changes of retinal and cerebral microvasculature is represented by arteriosclerosis, which is mostly age-related, affecting the brain and other various organs circulation. The severity of arteriosclerotic processes is also related to other cardiovascular and cerebrovascular risk factors, one of the most important ones being represented by hypertension and diabetes [27]. CSVD is diagnosed based on brain imaging features that rely on recent small subcortical infarcts, white matter hyperintensities, lacunas, cerebral microbleeds, enlarged perivascular spaces, and cerebral atrophy, all of them related to specific clinical neurological syndromes, according to their topography [27]. According to Thomson et al., CSVD is a systemic disorder, and the exact mechanism behind these small vessels lesions is still under research [28]. Existing imaging methods cannot yet assess the cerebral microvasculature pattern. Due to their similar patter, retinal vessel appearance and analysis can constitute a surrogate biomarker for cerebral microcirculation characteristics [29].

Blood vessels map obtained by fundus photography serve for retinal vessels segmentation that can further divided into thick or thin according to their diameter. After this classification, ophthalmologic characteristics are evaluated by the same software, regarding the blood vessels tortuosity (curvature arch length), and junctional pattern (number of terminal points, number of bifurcation points and number of crossing points). Each image of fundus photography is processed, and the traits were divided into several classes. By Compound Hierarchy of Algorithms Representing Morphology (CHARM) method, Orlov at al. reported significant changes of retinal vasculature related to the aging process [30]. CHARM method also revealed a strong correlation between retinal vascular pattern and blood pressure, the diameters and junctional pattern being negatively correlated with blood vessels, since tortuosity was positively correlated with blood pressure values ($p<0.05$) [30].

There are strong suggestions regarding the association of cerebral vessels branching pattern and retinal vascular features. Branching retinal pattern was also suggested to be associated with small vessels diseases subtype [31].

The Cerebral Autosomal Dominant Arteriopathy represents one of the cerebral vascular disease affecting small vessels (small penetrating cerebral and leptomeningeal arteries) with Subcortical Infarcts and Leucoencephalopathy (CADASIL). The pathophysiological mechanism of this ischemic disorder is represented by arterial wall lesions (mostly determined by lipohyalinosis). This process has, as a consequence, thickening of the arterial wall and subsequent stenosis. By structural changes of the arterial wall, there is an increased risk of microthrombosis, and obstruction of the vessels lumen with cerebral ischemia [32]. CADASIL is the most common cause of cerebral ischemia and vascular dementia in old adults. Patients with CADASIL have specific characteristic imagistic features and a higher frequency of migraine with aura [32,33]. Characteristic imagistic features consist in cerebral microbleeds and dilated Virchow–Robin spaces which represent early tissue changes and can be detected by magnetic resonance imaging (MRI) [33]. This hereditary disease consists of lesions of small cerebral vessels due to a genetic mutation that leads to the accumulation of cysteine residues in vessels wall that produces a dysfunction of transmembranal receptor and subsequent leukoencephalopathy and cerebral ischemia. In CADASIL, by fractal analysis of retinal vessels is possible to assess the brain vessels alteration, the branching pattern of retinal vessels being associated with cerebral vessels alteration (assessed by cranial MRI examination). No correlation was found between the duration and extension of brain microcirculation disease and the branching pattern of retinal vessels assessed by fractal analysis [33].

Fractal analysis of retinal vessels suggests that distinct features of vasculopathy can be associated with lacunar stroke, this type of stroke representing about 25% of total ischemic strokes [31]. Loos of branching complexity, assessed by fractal analysis of retinal vessels, was found to be related to aging and cerebral small vessels disease incidence [31,34]. Orlov et al. reported a correlation between the age of the patients and their blood pressure, observing a paucity of branching according to older age and high blood pressure [30]. Loss of complexity of retinal vasculature branching, junctional features, tortuosity, and length of collateral vessels is related to older age. The most sensitive parameter of retinal vessels morphological features is represented by tortuosity, which was reported to decrease with age. These results suggest that the aging process is associated with loss of microvasculature in retinal circulation and cerebral circulation either [30]. Besides hypertension, retinal vascular network in the elderly was either correlated with other cardiovascular risk factors such as diabetes mellitus [35,36]. Decreased vascular density and apoptosis of pericytes from microvasculature structure can be related to activation of renin-angiotensin-aldosteron system one of the most important pathophysiological mechanism implied in vascular lesion associated with hypertension and diabetes mellitus [37-39].

Geometrical details of retinal microvasculature, assessed by fractal analysis, were reported to be related to stroke incidence. This relationship is believed to be based on similarities of embryology, anatomy, and histology between retinal circulation and cerebral circulation. The retinal vasculature rarefaction can constitute a prognosis factor for stroke onset [35].

Lemmens at al. showed that the fractal dimensions (FD) of retinal vessels can be calculated as a monofractal or multifractal FD [40]. The complexity of retinal microvasculature make its more suitable for multifractal analysis that comprises FD_0, FD_1 and FD_2 which represents capacity dimensions, entropy dimensions and correlation dimensions [40]. According to Doubal et al., FD_0 would be the most appropriate measure for the complexity of the retinal microvasculature, because it appeared most sensitive to small vascular changes [31].

Conclusions

Fundus assessment by ophthalmoscopic examination and fractal analysis of retinal vasculature could constitute and very accessible method for prediction and evaluation of the relationship between retinal and cerebral circulation. Therefore, *in vivo* study of the retina by fundus examination may offer the opportunity for real-time evaluation of carotid system circulation, retinal, and cerebral perfusion. Therefore, fractal analysis of retinal vessels could be considered a valuable biomarker in cerebrovascular disease prognosion and diagnosis.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Wang SB, Mitchell P, Liew G, Wong TY, Phan K, Thiagalingam, et al. A spectrum of retinal vasculature measures and coronary artery disease. Atherosclerosis 2018;268:215-224. doi: 10.1016/j.atherosclerosis.2017.10.008.
2. McGrory S, Ballerini L, Doubal FN, Staals J, Allerhand M, Valdes-Hernandez MDC, et al. Retinal microvasculature and cerebral small vessel disease in the Lothian Birth Cohort 1936 and Mild Stroke Study. Sci Rep 2019; 9(1):6320. doi: 10.1038/s41598-019-42534-x.
3. Popovic N, Lipovac M, Radunovic M, Ugarte J, Isusquiza E, Beristain A, et al. Fractal characterization of retinal microvascular network morphology during diabetic retinopathy progression. Microcirculation 2019; e12531, doi: 10.1111/micc.12531.

4. Csincsik L, MacGillivray TJ, Flynn E, Pellegrini E, Papanastasiou G, Barzegar-Befroei N. Peripheral Retinal Imaging Biomarkers for Alzheimer's Disease: A Pilot Study. Ophthalmic Res 2018;59(4):182-192. doi: 10.1159/000487053.
5. Sng CC, Sabanayagam C, Lamoureux EL, Liu E, Lim SC, Hamzah H. Fractal analysis of the retinal vasculature and chronic kidney disease. Nephrol Dial Transplant 2010;25(7):2252-2258. doi: 10.1093/ndt/gfq007.
6. Birkhoff WAJ, van Manen L, Dijkstra J, De Kam ML, van Meurs JC, Cohen AF. Retinal oximetry and fractal analysis of capillary maps in sickle cell disease patients and matched healthy volunteers. Graefes Arch Clin Exp Ophthalmol 2020;258(1):9-15. doi: 10.1007/s00417-019-04458-0.
7. Al-Sheikh M, Phasukkijwatana N, Dolz-Marco R, Rahimi M, Iafe NA, Freund KB, et al. Quantitative OCT Angiography of the Retinal Microvasculature and the Choriocapillaris in Myopic Eyes. Invest Ophthalmol Vis Sci. 2017;58(4):2063-2069. doi: 10.1167/iovs.16-21289.
8. Liberek I, Chaberek S, Anielska E, Kowalska K, Ostrowski K. Symmetry of retinal vessel arborisation in normal and amblyopic eyes. Ophthalmologica 2010;224(2):96-102. doi: 10.1159/000235826.
9. Kumar RS, Anegondi N, Chandapura RS, Sudhakaran S, Kadambi SV, Rao HL, et al. Discriminant Function of Optical Coherence Tomography Angiography to Determine Disease Severity in Glaucoma. Invest Ophthalmol Vis Sci. 2016;57(14):6079-6088. doi: 10.1167/iovs.16-19984.
10. Azemin MZ, Kumar DK, Wong TY, Wang JJ, Mitchell P, Kawasaki R, et al. Age-related rarefaction in the fractal dimension of retinal vessel. Neurobiol Aging 2012;33(1):194.e1-4. doi: 10.1016/j.neurobiolaging.2010.04.010.
11. Wu F, Liu Y, Zhang K. Examination of the Retina. N Engl J Med. 2015;373(25):2484. doi: 10.1056/NEJMc1511801.
12. Bulboacă AE, Stănescu IC, Bolboacă SD, Bulboacă AC, Bodizs GI, Nicula CA. Retinal Nerve Fiber Layer Thickness and Oxidative Stress Parameters in Migraine Patients Without Aura: A Pilot Study. Antioxidants 2020 ;9(6):E494. doi: 10.3390/antiox9060494.
13. Bulboacă AE, But V, Bolunduț D, Bulboacă A, Bolboacă SD. Characterization of retinal vessels by fractal analysis: its importance in pathology. Applied Medical Informatics 2019;41(Suppl. 1):31.
14. Campbell JP, Zhang M, Hwang TS, Bailey ST, Wilson DJ, Jia Y, et al. Detailed Vascular Anatomy of the Human Retina by Projection-Resolved Optical Coherence Tomography Angiography. Sci Rep 2017;7:42201. doi: 10.1038/srep42201.
15. Theelen T, Teussink MM. Inspection of the Human Retina by Optical Coherence Tomography. Methods Mol Biol. 2018;1715:351-358. doi: 10.1007/978-1-4939-7522-8_26.
16. Kirkwood BJ. Anatomy of the retina. Insight 2012;37(4):5-8.
17. Cheung CY, Zheng Y, Hsu W, Lee ML, Lau QP, Mitchell P, et al. Retinal vascular tortuosity, blood pressure, and cardiovascular risk factors. Ophthalmology 2011;118(5):812-818, doi: 10.1016/j.ophtha.2010.08.045.
18. Abramoff MD, Garvin MK, Sonka M. Retinal imaging and image analysis. IEEE Reviews in Biomedical Engineering 2010;3:169-208. doi10.1109/RBME.2010.2084567.
19. Hoon M, Okawa H, Della Santina L, Wong RO. Functional architecture of the retina: development and disease. Prog Retin Eye Res 2014;42:44-84. doi: 10.1016/j.preteyeres.2014.06.003.
20. Lee J, Zee BCY, Li Q, Detection of Neovascularization Based on Fractal and Texture Analysis with Interaction Effects in Diabetic RetinopathyPLoS One. 2013; 8(12): e75699. doi: 10.1371/journal.pone.0075699
21. Ben-Jacob E, Garik P. The formation of patterns in non-equilibrium growth. Nature 1990; 343:523–30.
22. Pietronero L, Erzan A, Evertsz C. Theory of Laplacian fractals: diffusion limited aggregation and dielectric breakdown model. Physica A 1988;151:207-245.
23. Murray CD. The physiological principle of minimum work: The vascular system and the cost of blood volume. Proc Natl Acad Sci USA 1926;12(3):207-214. doi: 10.1073/pnas.12.3.207.

24. Cassot F , Lauwers F, Sylvie Lorthois S, Puwanarajah P, Duvernoy H. Scaling Laws for Branching Vessels of Human Cerebral Cortex. Microcirculation 2009;16(4):331-44. doi: 10.1080/10739680802662607.
25. Petty GW, Brown RD, Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. Stroke 2000;31(5):1062-1068.
26. Li Q, Yang Y, Reis C, Tao T, Li W, Li X. Cerebral Small Vessel Disease. Cell Transplant 2018;27(12):1711-1722. doi: 10.1177/0963689718795148.
27. Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH , Meschia JF. CNS Small Vessel Disease: A Clinical Review. Neurology 2019;92(24):1146-1156. doi: 10.1212/WNL.0000000000007654.
28. Thompson CS, Hakim AM. Living beyond our physiological means: small vessel disease of the brain is an expression of a systemic failure in arteriolar function: a unifying hypothesis. Stroke 2009;40:322-330.
29. Doubal FN, de Haan R, MacGillivray TJ, Cohn-Hokke PE, Dhillon B, Dennis MS, et al. Retinal arteriolar geometry is associated with cerebral white matter hyperintensities on magnetic resonance imaging, Int J Stroke 2010;5(6):434-439. doi: 10.1111/j.1747-4949.2010.00483.x.
30. Orlov NV, Coletta C, van Asten F, Qian Y, Ding J, AlGhatrif M, et al. Age-related Changes of the Retinal Microvasculature. PLoS One 2019;14(5):e0215916. doi: 10.1371/journal.pone.0215916.
31. Doubal FN, MacGillivray TJ, Patton N, Dhillon B, Dennis MS, Wardlaw JM. Fractal Analysis of Retinal Vessels Suggests That a Distinct Vasculopathy Causes Lacunar Stroke. Neurology, 2010;74(14):1102-1127. doi: 10.1212/WNL.0b013e3181d7d8b4.
32. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. CADASIL. Lancet Neurol 2009;8:643-653.
33. Cavallari M, Falco T, Frontali M, Romano S, Bagnato F, Orzi F. Fractal Analysis Reveals Reduced Complexity of Retinal Vessels in CADASIL. PLoS One 2011;6(4):e19150. doi: 10.1371/journal.pone.0019150.
34. Azemin MZ, Kumar DK, Wong TY, Kawasaki R, Mitchell P, Wang JJ. Robust methodology for fractal analysis of the retinal vasculature. IEEE Trans Med Imaging 2011;30(2):243-50. doi: 10.1109/TMI.2010.2076322.
35. Arnould L, Binquet C, Guenancia C, Alassane S, Kawasaki R, Daien V, et al. Association between the retinal vascular network with Singapore "I" Vessel Assessment (SIVA) software, cardiovascular history and risk factors in the elderly: The Montrachet study, population-based study. PLoS One 2018;13(4):e0194694 Epub 2018/04/04. 10.1371/journal.pone.0194694.
36. Guo VY, Chan JC, Chung H, Ozaki R, So W, Luk A, et al. Retinal Information is Independently Associated with Cardiovascular Disease in Patients with Type 2 diabetes. Sci Rep 2016;6:19053.
37. Puro DG, Retinovascular physiology and pathophysiology: new experimental approach/new insights. Prog Retin Eye Res 2012;31:258-270. doi: 10.1016/j.preteyeres.2012.01.001.
38. Poplin R, Varadarajan AV, Blumer K, Liu Y, McConnell MV, Corrado GS, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning, Nat Biomed Eng 2018;2(3):158-164. doi: 10.1038/s41551-018-0195-0.
39. Azemin MZC, Kumar DK, Wong TY, Wang JJ, Mitchell P, Kawasaki R, et al. Age-related rarefaction in the fractal dimension of retinal vessel. Neurobiol Aging 2012;33(1):194.e1-4. doi: 10.1016/j.neurobiolaging.2010.04.010.
40. Lemmens S, Devulder A, Keer KV, Bierkens J, De Boever P, Stalmans P, Systematic Review on Fractal Dimension of the Retinal Vasculature in Neurodegeneration and Stroke: Assessment of a Potential Biomarker Front. Neurosci., 2020, doi.org/10.3389/fnins.2020.00016.