Usefulness of retinal optical coherence tomography angiography evolution in cases of systemic diseases

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ABSTRACT

Assessment of retinal blood vessels in ophthalmoscopy fundus examination is a basic and standard exam in case of systemic diseases such as: diabetes mellitus, hypertension, arteriosclerosis and kidney disease. The introduction of retinal optical coherence tomography angiography (OCTA) enables the imaging of small retinal blood vessels in a highly precise and repeatable manner providing high resolution images. This review presents the changes in retinal blood vessels in the course of systemic disease based on optical coherence tomography angiography and the clinical application of this method. In the future, OCTA, as an accurate, routine and non-invasive method, may become commonly used not only in ophthalmology but also in other fields of medicine such as diabetology, hypertensiology, cardiology, rheumatology, pediatrics and others.

KEY WORDS: retinal optical coherence tomography, optical coherence tomography angiography, systemic disease, diabetes mellitus, hypertension, coronary heart disease, sickle cell disease, systemic lupus erythematosus, obstructive sleep apnea syndrome.

Systemic diseases such as diabetes, hypertension and arteriosclerosis, the pathogenesis of which involves changes in blood vessels require systematic monitoring of the status of vasculature [1, 2]. Fundus examination is a basic, routine and simple examination type which allows for intravital assessment of blood vessel changes in the human body [2]. It is assumed that the status of vasculature in the entire body is equivalent to the condition of the retinal blood vessels [3]. Therefore, based on retinal blood vessel examination results it is possible to assess the progression of a systemic diseases [3].

Fluorescein angiography (FA) is a commonly applied method of precise blood vessels assessment. However, the method has certain limitations as it requires intravenous administration of a contrast medium, which may lead to an allergic reaction, vomiting and cardiovascular adverse events [4-7]. Moreover, fluorescein angiography is able to image primarily the blood vessels located in the superficial retinal layer [6, 7].

The introduction of retinal optical coherence tomography (OCT) in 1991 [8] marked a breakthrough in ophthalmological diagnostics [4, 9]. OCT is one of the only non-invasive and contactless imaging methods which provides a detailed image of the layered retinal structure in vivo [9]. The method is based on interferometry so image acquisition requires detection and analysis of light rays reflected and scattered by the ocular tissues [9]. Tidal fluctuations of the signal level vary in intensity and frequency depending on the amount of light reflected by an ocular structure and the length of the optical path, respectively. Nowadays, the method has become a standard of care in ophthalmological practice, which enables clinicians to assess ocular structures and their function in real time [10]. OCT is used for qualitative assessment of morphology, thickness and anatomical changes in the retina as well as imaging of the optic nerve structure. OCT also enables clinicians to detect and quantify pathological changes such as oedema, intraretinal and subretinal fluid [10].

In 2016, optical coherence tomography angiography was presented as a new and promising method of imaging the retinal vasculature. OCTA scans are acquired following the analysis of light reflected by vascular and neurosensory tissues of the retina [4, 9]. The method is based on detection of erythrocyte movement in the lumen of blood vessels. Tidal signal variations in a sequence of scans, caused by particle movement, generate contrast, which is subsequently used to generate an image of the retinal vasculature [4-6, 9, 11]. During the examination, it is required to perform multiple

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scans of the same retinal zone in order to detect movement and generate an image of a vascular area. OCTA is able to generate repeatable, reliable and high resolution images [9]. The method provides numerical data concerning perfusion in the blood vessels and avascular zones in the imaged retinal area [5]. Blood vessel density is defined as the percentage of blood vessel surface area in which erythrocyte movement is detectable, as compared to the total field of observation [12]. The device is able to generate blood vessel density maps in which vascular and avascular zones are presented in contrasting colors [5, 11]. As opposed to fluorescein angiography, OCTA provides a high-resolution visualization of blood vessel status in various retinal layers, including the superficial and deep plexus [4-6, 9]. None of the earlier diagnostic methods, including fundus examination and fluorescein angiography, was able to provide data concerning the depth of vascular changes [5, 6, 9].

Unfortunately, OCTA also has some limitations as compared to fluorescein angiography. OCTA does not enable dynamic visualization of changes occurring in the retinal vessels and thus, it is impossible to assess the severity of exudates, vessel refilling rate and the area of leakage. OCTA examination allows for imaging of the retina only in a defined small field, and, in case of fluorescein angiography, a wide field function is available [6]. In ambiguous cases, OCTA image in combination with more conventional methods, such as fluorescein angiography, may be quite useful.

OCTA is able to reliably visualize vascular changes such as microaneurysms, neovascularization, vascular anomalies, perfusion impairments and changes in the foveal avascular zone [9]. Data from OCTA scans may be used as diagnostic markers as well as help physicians assess disease progression and control patient's response to treatment [5]. The method does not require administration of a contrast medium and therefore does not carry any risk of contrast-related complications, which allows for multiple re-examinations.

However, it must be mentioned that the method also has certain disadvantages. OCTA, as a new technology, is not validated, there are no universal standards applicable to examination results [6]. Each device supplied by a different manufacturer uses different types of scanning algorithms, and the test areas are also different [7]. Imaging artifacts, which may occur during an OCTA examination, may consequently hamper the interpretation of results [13]. The conclusions drawn from OCTA images should be interpreted with regard to the capabilities of the device used in the examination and several tests should be repeated using the same device to allow for results comparison [7].

Nowadays, OCTA has become the standard, commonly performed additional test in ophthalmological practice for the assessment of central retinal vein occlusion (CRVO), age-related macular degeneration (AMD), central serous retinopathy (CSR), uveitis, neovascularization and telangiectasia [7, 9 ,14]. However, to date the method has not been routinely utilized by practitioners in other fields of medicine to assess the status of blood vessels in cases of systemic diseases. The purpose of this article is to present the applications of OCTA in assessment and analysis of retinal vasculature changes in cases of systemic diseases.

The retina is a structure with one of the highest oxygen demand levels in the human body, which makes it highly susceptible to irreversible damage as a consequence of oxygen deficiency [14]. In the available literature, the authors conclude that oxygen demand in the macular region of the retina actually exceeds that of the brain [7, 14]. Therefore, the status of the macular vasculature may potentially reflect the vascular status of the brain itself. The image of the retinal vasculature may reflect the condition of the micro vessels in the vascular beds of other organs, thus potentially representing their status and function level.

The available study results regarding retinal blood vessels of patients with systemic diseases indicate that in the future it might be possible to use OCTA for diagnostics and disease control, even as early as the pre-symptomatic stage. Numerous authors claim that OCTA is an interdisciplinary method which should be utilized in fields such as diabetology, cardiology, hypertensiology, pulmunology, neurology, nephrology and rheumatology [5, 6, 9, 15, 16].

DIABETES MELLITUS

The most common reason why patients with systemic diseases report for dilated fundus examination is diabetes mellitus [17]. The number of diabetic patients in the global population is estimated at 415 million [18]. Ocular complications of diabetes include diabetic retinopathy (DR) which seems to be the leading cause of vision loss and blindness globally [9, 19]. It is highly probable that routine ophthalmoscopic fundus examination allows for detection of the disease at a relatively advanced stage [20]. A superior feature of OCTA is the ability to detect early vascular changes which might not have been visible during fundus examination or fluorescein angiography [7, 9]. The characteristics OCTA results in cases of diabetes include capillary remodeling, microaneurysms, focal blood vessel constrictions, impaired perfusion, neovascularization and the loss of capillaries. Those processes result in enlargement of the foveal avascular zone (FAZ), reduction in vessel density in the superficial capillary plexus (SCP) and the deep capillary plexus (DCP) [4, 21]. Numerous studies presenting the qualitative and quantitative data on the application of OCTA in diabetic patients have shown that the vascular changes become detectable prior to the diagnosis of diabetic retinopathy based on a ophthalmoscopic examination [19, 21–24].

Dimitrova *et al.* [19] analyzed the results of OCTA in 29 cases of type 2 diabetes mellitus without diabetic retinopathy. The authors reported that the parafoveal vessel density in the superficial capillary plexus was significantly reduced (44.35% ±13.31%) and the foveal avascular zone was significantly enlarged (0.37 ±0.11 mm^2) in subjects with diabetes mellitus, as compared to controls (51.39% ±13.05%, $p = 0.04$; 0.31 ±0.10 mm^2, $p = 0.02$). The parafoveal vessel density in the deep capillary plexus was also reduced (31.03% ±16.33%),

as compared to controls (41.53% ±14.08%), and this parameter was correlated with the subjects' age, systemic blood pressure and ocular perfusion pressure.

Niestrata-Ortiz *et al.* [22] analyzed OCTA results in 112 pediatric patients with type 1 diabetes mellitus without diabetic retinopathy and observed a statistically significant increase in the size of foveal avascular zone in the superficial capillary plexus and deep capillary plexus of the study subjects, as compared to controls. The authors have reported more pronounced changes in the size of foveal avascular zone in the deep capillary plexus (521.8 μm^2 vs. 409.8 μm^2), as compared to the superficial capillary plexus (304.76 μm^2 vs. 286.45 μm^2).

Similar results have been reported by authors of subsequent studies based on their own OCTA analyses in children with type 1 diabetes mellitus without diabetic retinopathy [21, 23, 24]. They observed reduced retinal vessel density before any changes in the fundus became noticeable.

OCTA may also be useful in patients with prior diabetic retinopathy-related changes as the method is able to define the neovascularization area and subsequently perform an accurate quantitative assessment of the affected area in the retina [4, 22].

Pan *et al.* [25] assessed 35 subjects with diagnosed proliferative diabetic retinopathy (PDR). Their analysis has identified the following neovascularization-related changes: 75 new vessels elsewhere (NVE), 35 new vessels on the optic disc (NVD) and 12 intraretinal microvascular abnormalities (IRMA). OCTA allowed the researchers to visualize the microstructure of the new pathological blood vessels (neovascularization), identify their origin and define their location.

Mané *et al.* [26] analyzed vascular changes in subjects with diabetic macular edema and observed a lack of capillary perfusion around the cysts in the edematous area of the superficial capillary plexus (71% of subjects) and the deep capillary plexus (96% of subjects). Vessel density has been reduced significantly in both plexuses and, importantly, it remained unchanged following the resolution of the macular edema, which signifies that perfusion has not reoccurred in the affected areas.

The authors of the available reports claim that the vascular changes are more advanced in the deep capillary plexus than in the superficial capillary plexus [4, 19, 21, 22, 27]. The extent of vascular changes in the deep capillary plexus is related to concomitant macular oedema and disorganization of the deeper retinal layers [1]. This might indicate the direction of the neovascularization process, which probably begins in the deeper retinal layers and develops towards the superficial layers, which may subsequently be followed by manifestation of clinical features of diabetic retinopathy, including macular oedema [22].

According to Sanhu *et al.* [28], the sensitivity of OCTA in diagnosing diabetic retinopathy is as high as 94.3% while its calculated specificity is 87%.

Based on the sources discussed above, it seems that the results of blood vessel status analysis using OCTA may constitute potential markers for diabetic retinopathy risk assessment. In order for OCTA to be used in the future as an additional indicator for the choice of therapy and medication in diabetes treatment, additional research is required on a large group of subjects with an assessment of the repeatability, sensitivity and specificity of the method.

HYPERTENSION

It is commonly known that patients diagnosed with hypertension are prone to vascular changes affecting the entire body [29]. The consequences of damage to retinal vasculature caused by high blood pressure may be observed during fundus biomicroscopy, oftentimes prior to any apparent damage in the vital organs [30, 31].

Retinal vascular density studies using OCTA in 57 patients with chronic hypertension without hypertensive retinopathy were analyzed by Hua *et al.* [32]. In patients with chronic hypertension, parafoveal vascular density in the superficial plexus was significantly lower than in healthy subjects. There was no difference in the density of the vessels, in the deep plexus between the groups. In cases of chronic hypertension duration being longer than 10 years, the foveal avascular zone was larger than in healthy controls. In addition, inside disc capillary density and peripapillary capillary density was significantly lower in patients diagnosed with chronic hypertension than in healthy subjects.

Lee *et al.* [15] presented their study results related to retinal vessel changes in cases of hypertension. The authors performed OCTA in 85 subjects diagnosed with chronic hypertension (CHTN) and divided the study population into two groups, depending on the presence of clinical changes in the fundus that is hypertensive retinopathy (HTNR). Subjects in Group A had chronic hypertension for more than 10 years without noticeable changes in the fundus while Group B included subjects with chronic hypertension and a prior diagnosis of hypertensive retinopathy. Lee *et al.* noticed reduced vessel densities in both groups of hypertensive subjects (Group A: 19.4 ±1.4 mm^{-1}; Group B: 19.8 ±1.6 mm^{-1}), as compared to healthy subjects in both control groups (Group C: 20.1 ±1.0 mm^{-1}; Group D: 21.8 ±0.8 mm^{-1}). In both study groups with hypertension, the foveal avascular zone was significantly enlarged (Group A: 0.35 ±0.05 mm^2; Group B: 0.36 0.03 mm^2), as compared to the controls (Group C: 0.30 ±0.07 mm^2; Group D: 0.29 ±0.06 mm^2). It is noticeable that in both groups of hypertensive subjects OCTA indicated comparable changes in the retinal microcirculation, regardless of the presence of clinical changes in the fundus characteristic of hypertensive retinopathy [15].

However, Donati *et al.* [33] based on a study of 30 patients with arterial hypertension, observed vascular changes only in the deep vascular plexus. The authors noted statistically significant lower values of parafoveal and whole image vascular density in the group of hypertensive patients as compared to healthy subjects. Statistically significant enlargement of the foveal avascular zone in the deep layers of the retina was noted only in the group of patients already treated for systemic hypertension as opposed to healthy subjects.

The same conclusions have been described by Chua *et al.* [34] who analyzed OCTA results in 77 cases of hypertension. The authors reported that patients with hypertension had a reduced retinal vessel density in the superficial capillary plexus and the deep capillary plexus, as compared to healthy subjects. The results of vessel density measurements were correlated with systolic blood pressure (SBP), mean arterial pressure (MAP) and the estimated glomerular filtration rate (eGFR).

Pascular-Prieto *et al.* [35] also noted reduced perfusion density in both superficial and deep plexus in hypertension. The study evaluated OCTA of 47 patients with hypertension and divided them into groups with low and very high cardiovascular risk. The authors noted statistically significant lower macular perfusion density in the deep and the superficial plexus among hypertensive patients in both cardiovascular risk groups, as compared to the control group.

Takayama *et al.* [36] analyzed retinal vessels of 206 patients with and without hypertension. The authors noted that foveal vessel density was significantly correlated with the grade of changes according to Keith-Wagener-Barker classification. The Keith-Wagener-Barker classification is a traditional, useful, and commonly used scale for assessing the grade of hypertensive retinopathy based on fundus examination [37]. According to the results of the above studies, the analysis of vascular changes using OCTA may be a potentially useful factor in diagnosing hypertension and for potential modification of therapy in such cases. However, this requires further thorough research with additional evaluation of subjects' clinical data.

CORONARY HEART DISEASE

Due to the fact that the caliber of the retinal blood vessels is comparable to those forming the coronary microcirculation, the results of blood vessels examination using OCTA may be representative of the status of the coronary arteries [16]. In order to investigate the relation between the changes in the retinal blood vessels and the coronary blood vessels, Wang *et al.* [16] analyzed examination results of 158 adult subjects diagnosed with coronary heart disease but without any concomitant vision loss. All the subjects underwent OCTA, including assessment of retinal blood vessel parameters, and coronary artery angiography. In the group of subjects with coronary heart disease, the authors confirmed vessel constriction in all branches of the coronary arteries. They have also noted a significant reduction in retinal vessel density in the parafoveal area (in both the superficial capillary plexus and the deep capillary plexus), as compared to healthy controls. It should be emphasized that patients with coronary heart disease had a denser vasculature in the outer retina, as compared to healthy controls, while the fovea vascular densities in the superficial capillary plexus and the deep capillary plexus did not differ significantly between the groups. Result analysis indicated that the changes in vascular density in all retinal areas, except for the fovea, were negatively correlated to constriction of the left coronary artery [16].

The above results suggest that, in cases of coronary heart disease, damage to the retinal vasculature may precede symptoms of retinopathy which are noticeable during ophthalmoscopy exams. Therefore, hopefully directed future research on larger patient groups and analysis of the correlation between OCTA results and other clinical parameters will make OCTA a useful method in monitoring and treatment of coronary heart disease.

SICKLE CELL DISEASE

Sickle cell disease (SCD) is a congenital blood disorder caused by abnormal structure of hemoglobin. In approximately 10% of cases, the underlying disease is concomitant with retinopathy which is usually diagnosed during fundus examination [38].

Roemer *et al.* [39] analyzed OCTA results for 19 eyes in 10 pediatric patients diagnosed with hemoglobin gene mutation and reported a reduced vessel density in the foveal region both in the superficial capillary plexus (25.8% vs. 32.5% $p < 0.001$) and the deep capillary plexus (22.6% vs. 26.4%, $p < 0.08$), as compared to controls. Significant vascular density changes have not been observed in the parafoveal region. The authors described enlarged foveal avascular zone in the group of subjects with sickle cell disease, as compared to controls (0.39 mm^2 vs. 0.27 mm^2, $p < 0.08$) and the parameter was correlated with the subjects' age in this group. Importantly, clinical changes characteristic of sickle cell retinopathy (SCR) were detected using ophthalmoscopic examination only in 8 out of 19 study eyes.

Equivalent conclusions were published by Pahl *et al.* [38] based on their own analysis [23]. The team have examined 32 eyes of 16 patients with sickle cell disease aged 10 to 19 years and found areas with reduced vessel density in the foveal regions of 6 eyes (both in the superficial capillary plexus and the deep capillary plexus). None of the subjects with sickle cell disease included in the analysis had their vascular abnormalities detected during prior slit lamp examinations [38].

At present, the available studies concerning the changes in OCTA in anemia are scarce and include small patient groups. However, in the future, OCTA might become a useful tool to detect anemia in suspicious cases, based on a prior retinopathy diagnosis.

OBSTRUCTIVE SLEEP APNEA SYNDROME

Changes in retinal vessel density may be affected by a number of factors, including oxygen deficiency which is the primary cause of complications in obstructive sleep apnea syndrome (OSAS) [12, 14, 40].

In their study, Yu *et al.* [12] included 69 patients diagnosed with obstructive sleep apnea syndrome based on their polysomnography results. The subjects were divided into three groups depending on their apnea-hypopnea index (AHI): normal-to-mild (apnea-hypopnea index < 15), moderate (≥ 15 to < 30) and severe (≥ 30). The group with severe obstructive sleep apnea syndrome showed a statistically significant reduction in vessel density both in the parafoveal (56.4%

±1.8 vs. 58.2% ±2.1) and the peripapillary region (63% ±3 vs. 66% ±2), as compared to the normal-to-mild severity group. Subjects with moderate obstructive sleep apnea syndrome, as compared to the normal-to-mild severity group, showed a reduction in vessel density only in the peripapillary region (63%± 3 vs. 66±2) but not observed in the parafoveal region. It should be emphasized that the subjects showed a relatively more significant vasculature reduction in the peripapillary rather than the parafoveal region. Each reduction of apnea-hypopnea index by 10 units was related to a 0.43% decrease in mean vessel density in the parafoveal region and a 0.63% decrease in the peripapillary region, respectively. Moreover, retinal vessel density showed a significant correlation with disease severity based on the apnea-hypopnea index and the lowest nocturnal peripheral oxygen saturation level (SpO_2) [12].

Similar results have been reported by Wang *et al.* [40] based on their proprietary analysis of 27 cases of obstructive sleep apnea syndrome. The authors reported that subjects with a more severe stage of obstructive sleep apnea syndrome (based on the apnea-hypopnea index) showed a reduced vessel density in the foveal and the peripapillary region, as compared to subjects with less severe underlying disease [40].

The same parameters of retinal vessel density were analyzed by Ye *et al.* [14] in a group of pediatric patients. The study participants were children aged 4 to 11 years with a confirmed diagnosis of obstructive sleep apnea syndrome due to pharyngeal tonsil hypertrophy. The authors measured the study parameters of retinal vasculature prior to and one month following the surgical treatment of pharyngeal tonsil hypertrophy (adenoidectomy). They have observed an increase in vascular density in the parafoveal region (both in the superficial capillary plexus and the deep capillary plexus) in children who underwent surgical treatment of obstructive sleep apnea syndrome. This indicates that increased oxygen supply is reflected by an increase in the diameter, density and area of blood vessels. It should be noted that the parameters related to vessel density in the peripapillary region were stable and remained unchanged both prior to and following the surgical intervention [14].

The authors assumed that the cause of the observed changes was chronic, intermittent, recurrent and transient hypoxia which occurred during the periods of apnea. Obstructive sleep apnea syndrome is characterized by chronic impairment of airflow in the upper airways during sleep, associated with hypoxia, acidosis and hypercapnia. Sudden blood flow fluctuations and changes in blood pressure lead to oxidative stress, inflammation, epithelial disorders and atherosclerosis [12, 14, 41].

The above results indicate that OCTA may be helpful in the decision-making process concerning surgical treatment of certain diseases. However, it is still a method lacking universal standards applicable to its results and thus it may only serve as an additional test.

SYSTEMIC LUPUS ERYTHEMATOSUS

Numerous systemic diseases are associated with changes in the blood vessels of the fundus [12, 16, 19, 22, 38, 42].

Usually, retinopathy secondary to systemic diseases is understood as abnormal changes caused by diabetes and hypertension, as discussed above. More rarely considered causes include systemic lupus erythematosus which is an autoimmune disease developing as a consequence of complex disorders in the immunological system leading to chronic inflammation of various tissues and organs [43]. The pathogenesis of retinopathy in systemic lupus erythematosus is believed to involve deposition of immunological complexes in the vascular walls, which leads to vasculitis and later results in vessel constriction [43].

Conigliaro *et al.* [44] analyzed changes in the retinal blood vessel using OCTA in 52 eyes of patients diagnosed with systemic lupus erythematosus. Subjects with systemic lupus erythematosus had significantly lower total vessel density, vessel density in the foveal region and vessel density in the parafoveal region in the superficial capillary plexus, as compared to their healthy counterparts. Changes in the retinal vasculature observed in cases of systemic lupus erythematosus were more pronounced in patients who had an additional diagnosis of nephritis. The authors reported negative correlation between the disease activity indicator and the total vessel density and vessel density in the parafoveal region (both in the superficial capillary plexus and the deep capillary plexus). It should be emphasized that the authors have observed a positive correlation between the chloroquine dose administered during therapy of the underlying disease and vessel density in the parafoveal region, both in the superficial capillary plexus and the deep capillary plexus [44].

OCTA, even in cases of this autoimmune disease, seems to be a useful method of assessing the severity of changes in the blood vessels of the eye.

SUMMARY

Based on the results published in the available literature, it may be concluded that OCTA provides a significant amount of useful information concerning the status of blood vessels, both in the retina and the entire body. Nowadays, there are ongoing studies in order to extend the use of OCTA in the management of systemic diseases which previously did not include assessment of the retinal vasculature. Further randomized studies involving larger patient groups and assessment of additional tests are necessary in order for practitioners to be able to consider the application of OCTA in diagnostics, monitoring and treatment of systemic diseases. In the future, OCTA, as a repeatable and non-invasive method which does not increase the treatment burden, may become commonly used not only in ophthalmology but also in other fields of medicine such as cardiology, rheumatology, diabetology, pediatrics, hypertensiology and others. The method may be expected to prove useful also in the management of a number of other diseases.

DISCLOSURE

The authors declare no conflict of interest.

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