Quantitative analysis of the choroid – A possible endpoint for uveitis?

As an intricate vascular network embedded in a stroma of connective tissues, fibroblasts, melanocytes, and leukocytes, the choroid primarily functions to nourish the outer retina and secrete growth factors.[1] It is also important in regulating intraocular pressure, thermoregulation, and emmetropization.[1] Being a thin layer of delicate vessels, any alterations in the choroid's anatomical integrity could potentially lead to functional impairments affecting itself and the retina. This is especially so in macular involving diseases like age-related macular degeneration, central serous chorioretinopathy, and posterior uveitis, which can compromise the central vision.[2-5] However, the progress of choroidal pathologies has been largely limited by the lack of reliable measures for in-vivo studies. Longitudinal studies of structural changes are essential to achieve better understanding of the progression and treatment response of various chorioretinal diseases.

Based on the modern image binarization techniques, researchers have described and developed a new biomarker known as choroidal vascularity index (CVI) to quantitatively analyze the choroidal vasculature in addition to choroidal thickness (CT) captured on optical coherence tomography (OCT) B scans and choriocapillaris layer scans of optical coherence tomography angiography (OCT-A). CVI represents the percentage of the choroid that is vascular, defined as the ratio of vascular luminal area to total choroidal area. CVI provides specific information about the choroid and choroid's vascular status with simultaneous quantification of the stroma (stromal area), enabling analysis of different choroidal components. Currently, the researchers are unable to comment on what is the ground truth of choroidal vascularity and which layer of choroidal vasculature is specifically affected in uveitis or any other chorioretinal disease. However, recently CVI studies have been producing statistically significant data with great consistency in uveitis.[4,5]

Histopathological studies based on postmortem samples have established the foundation knowledge about the choroid's microanatomy in great detail. However, those findings may not be truly representative of the choroid's *in vivo* status, due to the artifacts and shrinkage induced by the fixation process.[6] Through modalities such as indocyanine green angiography and fundus fluorescein angiography, visualization of the choroid in living patients was made possible. But nonetheless, these invasive techniques are far from ideal, due to their requirement of intravenous dye injection, rendering them less favorable for clinical follow-ups or longitudinal research studies. In addition, the en-face view also hindered the visualization of different layers of choroidal vessels, which are often best seen in cross sections. Furthermore, extravasation of dye from choriocapillaris has compromised the techniques' accuracy to a certain extent.[7] The problem with resolution was also encountered in ultrasonography. Despite bypassing media opacity, the fine choroidal vasculature could not be viewed with satisfactory clarity.[8] Ultrasound's operator dependence also made it less reliable for research purposes.

With the advent of OCT, the choroid can now be visualized in cross-sectional cuts.[9] The choroid is portrayed by a layer of pixels, situated inferior to line of bright pixels that denote the retinal pigmental epithelium. In detail, the choroidal stroma is represented by grey pixels, with interspersed black pixels representing the vessel lumens. OCT imaging is repeatable and noninvasive, hence ideal for long-term monitoring of patients in the clinical setting. Research wise, OCT paved a path for the reliable qualitative analysis of choroidal structure. However, the establishment of a quantitative parameter is essential to produce repeatable results that can be evaluated for statistical significance. More importantly, scientists and clinicians worldwide need a common language for choroidal health status.

In recent years, the scientific community has seen a surge in interests for choroidal biomarker research in field of uveitis.[4,5,10-15] Existing biomarkers such as CT are simple measurements obtainable using the in-built caliper functions of OCT machines and has been widely reported.[10] However, CT by itself is not truly representative of the choroid's complex architecture. Any fluctuations in thickness could be due to alterations in either the stroma or vasculature, which CT failed to specify. Furthermore, for a highly vascular structure like the choroid, the main value of architectural evaluation perhaps lies in the blood vessels. Therefore, quantitative parameters ought to be specific in describing any changes and produce repeatable results. CT, being one of the most widely studied parameters, has been reported widely in the literature.

CVI can provide greater insights to the structural alterations following primary analysis using CT. CVI is a parameter to be used in both research and clinical setting. Consistent relationships were demonstrated between CVI and the activity of various chorioretinal diseases. For instance, the choroids of patients with Vogt-Koyanagi-Harada disease demonstrated reduced CVI during clinical remission, with increased CVI during relapses.[11,12] Likewise, CVI studies on patients with birdshot chorioretinopathy and sympathetic ophthalmia also confirmed the structural alterations in the choroid.[13,14] CVI studies brought greater insights to the disease's pathogenesis by proposing a possible component of choroidal ischemia that may contribute to the poorer vision in certain patients. Future studies will aim to produce more robust data sets and demonstrate the consistency of such relationships. With such, clinicians might consider monitoring patients using OCT-based quantitative analysis using composite index of both CT and CVI for more in-depth analysis of the choroid.[15] Clinicians might even detect subclinical disease activity in at risk patients, allowing early treatment and interventions.

CVI should be regarded as an addition to the available biomarkers including CT for more comprehensive analysis, establishing a choroidal quantitative analysis panel.[15] For instance, The panel should also take into account the changes in luminal and stromal areas, which would provide information on the exact choroidal component affected by various pathologies. CVI should also make references with existing histopathological or angiographic studies to further validate itself. The choroidal modifications, if any, could lead to changes vessel quantity, or both diameter and quantity. It would be essential to make reference with previous angiographic or histopathological studies of diseased choroids for validation.[15]

Application of choroidal tool in the clinical practice is limited due to certain challenges. Accurate analysis requires high-quality

OCT images. Despite better image resolution with each generation of OCT, the visualization of the choroid may still be inevitably affected by various factors. For example, inflammatory conditions such as Vogt-Koyanagi-Harada disease results in exudation that may compromise image resolution. Patient factors such as eye movements during the scan and media opacities like cataract may further influence the final image.

Applicability of CT and CVI data in the general population awaits further validation. Most of the studies are based on Asian populations, with small sample sizes and short follow-up periods. However, such issues are unavoidable for a budding field of science. Currently, both CT and CVI are regarded as a promising biomarker and a potential tool to monitor disease progression. Studies have demonstrated consistency in producing significant findings, leading to a greater prominence of CVI in choroidal research. For example, promising results have been demonstrated in the study published in the current issue, where authors have demonstrating changes in CT and CVI at various stages of the disease.

Though CVI has tremendous potential as a biomarker, its reliance on manual analysis remains one of the biggest limitations. Although proficiency can be improved through analyzing more images, segmenting and binarizing images one by one no doubt slows the progress of large sample analysis. In the daily clinical setting, clinician also might not have time to analyze every image. A unique automated algorithm for CT and CVI analysis, which can possibly be integrated into individual OCT machines as a in-built software, allowing immediate analysis upon scanning can be a useful tool in armamentarium of a uveitis specialist or medical retina specialist.

Lastly, more studies are required to prove CVI's applicability in various forms of uveitis to establish it as a possible end point for uveitis FDA is looking for, which we believe is a an essential global effort. We urge for multinational, multicenter collaboration to produce large sample longitudinal studies of different uveitic entities and demonstrate the true choroidal changes over time to establish choroidal tool as a possible end point. CVI should not be simply viewed as a biomarker, but more as a technique that will revolutionize choroidal structural analysis and have significant impact on clinical practice and clinical trials. Future studies should aim to produce software with fully automated algorithm that can be used for large samples and possibly volumetric study. Such software could also be integrated onto individual OCT machines for practical purposes and for it to be used in clinical trials.

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