• Investigation •

Comparison of choroidal vessel thickness in children and adult eyes by enhanced-depth imaging optical coherence tomography imaging

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Abstract

• AIM: To evaluate choroidal thickness, medium choroidal vessel thickness (MCVT) and large choroidal vessel thickness (LCVT) in normal children and adult subjects.

• METHODS: Manual measurements of subfoveal choroidal thickness (SFCT), MCVT and LCVT at subfoveal and 750 μm nasal and temporal to fovea locations were completed on enhanced-depth imaging optical coherence tomography (EDI-OCT) scans of normal children and adult subjects.

• RESULTS: Fifty adult and fifty-seven child subjects were included in the study (including 80 adult and 103 child eyes). Mean (±SD) SFCT of adult and children eyes in the study was 309.3±95.7 μm and 279.3±50.4 μm respectively. SFCT and subfoveal MCVT in adult eyes were significantly more than children (*P*=0.01 and *P*≤0.0001 respectively).

• CONCLUSION: There is choroidal thickening with associated thickening of medium choroidal vessels in adults, suggesting that there is alteration in choroidal vasculature with ageing.

• **KEYWORDS:** choroid; ageing; optical coherence tomography; vasculature; thickness

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INTRODUCTION

Visualization of the choroid using optical coherence tomography (OCT) has enabled the characterization of choroidal structure in several disease processes[1-2]. Developments in OCT technology, including enhanced depth imaging OCT (EDI-OCT), has facilitated the evaluation of choroidal morphology. This includes the description of choroidal structure, identification of choroidal vasculature and improved precision of OCT-derived choroidal thickness measurements[3-5].

Analysis of OCT-derived choroidal thickness measurements has revealed that there is alteration in choroidal thickness in a range of retinal diseases [including central serous chorioretinopathy (CSC), diabetic macular edema and age-related macular degeneration][6-8]. It has been suggested that this may be due to modification of stromal and/or vascular structures within the choroid. Indeed, thickening of choroidal vessel layers may in itself reflect an alteration in choroidal vascular permeability. Assessment of choroidal vascularity using OCT has revealed there are particular alterations in choroidal vessels in a range of diseases including diabetic retinopathy and CSC[9-10]. Furthermore, OCT analysis of large and small choroidal vessel thickness has been used to evaluate choroidal vascularity in chorioretinal disease[2,5].

OCT-derived choroidal thickness measurements appear to be different in children compared to adults and may not necessarily reflect the same alteration in diseases that has previously described in adult eyes[11]. Previous studies have investigated choroidal thickness measurements in pediatric populations, but determination of any association with choroidal vasculature, particularly change in large and small vessel choroidal vascular layers is needed. It is important

to consider that these choroidal thickness measurements in children may be associated with a range of factors including changes in axial length, refractive status and the particular age of the children themselves[11-13]. Furthermore, new research suggests that non-invasive imaging such as OCT may be valuable in the evaluation of systemic disease as choroidal thickness appears to alter in response to many conditions including hematological disease and obesity[14-15].

Analysis of individual choroidal layer thicknesses in children may help to understand both the structural changes associated with ageing as well as the assessment of chorioretinal disease in children. The aim of this study is to evaluate the difference between EDI-OCT derived choroidal thickness and vascular layer thickness measurements in healthy children and adult eyes.

SUBJECTS AND METHODS

Retrospective analysis of data collected from a prospective normative database of all subjects [adult and children (less than 18y of age)]. Parents/guardians of underage participants and all adult participants gave written informed consent prior to inclusion in the study. The study was approved by the local ethics committee (Smt. Kanuri Santhamma Retina Vitreous Centre, L V Prasad Eye Institute, Hyderabad, India) and adhered to the tenets set forth in the Declaration of Helsinki.

Study Population Inclusion criteria was healthy adults and children with refractive error of ±3 D and axial length less than 26 mm. EDI-OCT images of healthy adult and child subjects were acquired from normative database in identical resolution and in Joint Photographic Experts Group (JPEG) format. Exclusion criteria included history of active or previous retinal or chorioretinal disease, media opacity preventing adequate fundal imaging, previous ocular surgery (other than cataract surgery) and any other significant ocular comorbidity that had previously been noted.

SD-OCT Imaging Protocol All subjects underwent EDI-OCT imaging of the macula using DRI-OCT® (Topcon, Tokyo, Japan) by an experienced optometrist. High quality images with signal strength of no less than 15 dB were included. Best corrected visual acuity (BCVA), medical history and history of any previous ocular treatment was obtained from medical records.

Manual OCT Measurements All manual measurements were made using callipers on the Image J software (a publicly available image processing program developed by Wayne Rashand, National Institute of Health, Bethesda, Maryland, USA; available at: http://rsb.info.nih.gov/ij/index.html) by a single observer with an intra-observer repeatability of 0.92 to 0.99 for all measurements made. Choroidal thickness was defined as the perpendicular between the Bruch's membrane and the choroid-scleral interface and was measured at the fovea (subfoveal choroidal thickness, SFCT) as well as 750 μm nasal and temporal to the fovea.

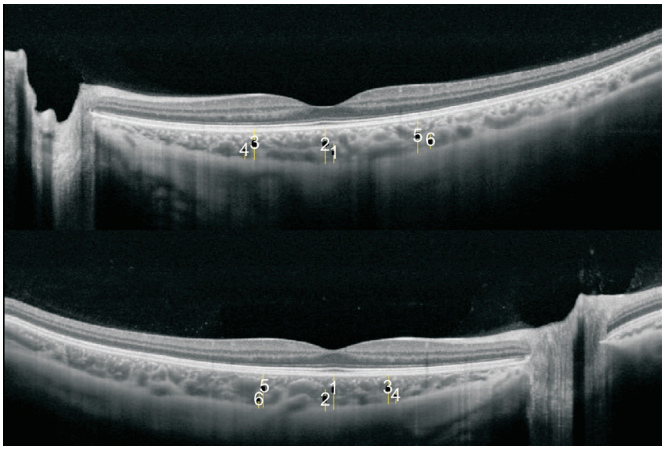

Figure 1 Manual enhanced-depth imaging optical coherence tomography derived choroidal and choroidal vessel thickness measurements in andult eyes (top) and child eyes (bottom) Yellow lines show manual measurements made (1 subfoveal choroidal thickness, 2 subfoveal large choroidal vessel thickness, 3 temporal choroidal thickness, 4 temporal large choroidal vessel thickness, 5 nasal choroidal thickness, 6 nasal large choroidal vessel thickness.

Large choroidal vessels were identified on EDI-OCT as vessels with diameter of more than 100 μm (as previously described by Branchini *et al*[5]). Large choroidal vessel thickness was measured between the innermost aspect of large choroidal vessels to retinal pigment epithelium (RPE). Medium choroidal vessel thickness (inclusive of medium choroidal vessel and choriocapillaris) was defined as the difference between choroidal thickness and large choroidal vessel thickness. Both large and medium choroidal vessel thickness were obtained at the fovea and 750 μm nasal and temporal to the fovea. Figure 1 demonstrates OCT measurements of choroidal thickness and choroidal vessel thickness made in this study.

Statistical Analysis All statistical analyses were performed using GraphPad Prism V7. Mean (±SD) of thickness of choroidal thickness, large and medium choroidal vessel thickness. *t*-test was used to compare thickness measurements at each location. ANOVA and post-hoc Tukey test was used for age-stratified analysis. Generalized estimating equation was used to limit co-linear artifacts.

RESULTS

Subject Characteristics Fifty adult and fifty-seven child subjects were included in the study (including 80 adult and 103 child eyes). The mean age of children and adults in the study was 9.7±3.3y and 50.7±18.5y respectively. There was no significant difference between the mean spherical equivalent between child and adult eyes included in the study. Demographics of both adult and children included in the study are shown in Table 1. Patients with refractive error of more than ±3 D were excluded from this study. There was no significant correlation (spearman correlation coefficient range r=-0.28, nasal choroidal thickness to r=0.14 SFCT, all P>0.05) between refractive error and choroidal thickness, large and

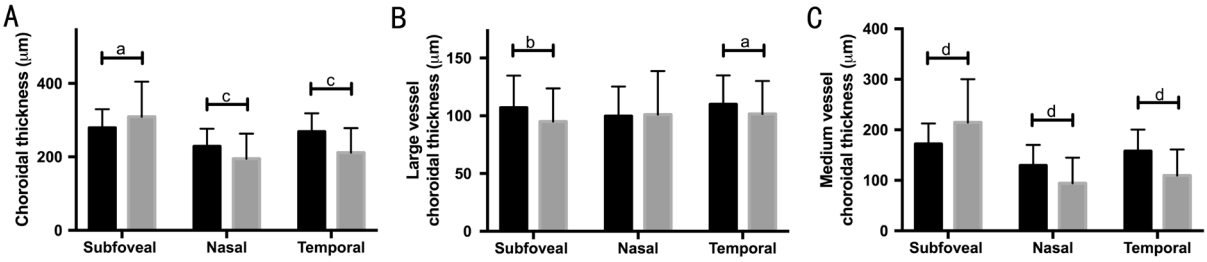

Figure 2 Choroidal thickness measurements in child and adult eyes EDI-OCT derived measurements of choroidal thickness (A), large choroidal vessel layer thickness (B) and medium choroidal vessel layer thickness (C) at subfoveal and 750 μm nasal and temporal to the fovea in child (black) and adult (grey) eyes. *t*-test: $^{a}P\leq 0.05$; $^{b}P\leq 0.01$; $^{c}P\leq 0.001$; $^{d}P\leq 0.0001$.

Table 1 Subject demographics of adult and child eyes mean±SD

Parameters	Children	Adult
Age, y	9.7±3.3	50.7±18.5
Male/Female, *n* (%)	43 (75)/14 (25)	25 (50)/25 (50)
Spherical equivalent, dioptres	+0.33±1.67	+0.1±0.9

medium choroidal vessel thickness (at subfoveal, nasal and temporal locations).

Analysis of EDI-OCT Choroidal Thickness Measurements EDI-OCT derived choroidal thickness and vessel layer thickness are shown in Figure 2.

Choroidal thickness Mean SFCT of adult and children eyes in the study was 309.3±95.7 μm and 279.3±50.4 μm respectively. SFCT in adult eyes was significantly more than children (P=0.01; Figure 2A). Nasal and temporal choroidal thickness in children however was significantly larger than in adults (P=0.0003 and P<0.0001, respectively).

Large choroidal vessel thickness Mean subfoveal large choroidal vessel thickness of adult and children eyes in the study was 95.1±28.7 μm and 107.1±27.8 μm, respectively. Subfoveal large choroidal vessel thickness and temporal large choroidal vessel thickness of child eyes was significantly larger than adult eyes (P=0.005 and 0.03, respectively; Figure 2B). There was no significant difference in nasal large choroidal vessel thickness between adult and child eyes (P=0.81).

Medium choroidal vessel thickness Mean subfoveal medium choroidal vessel thickness of adult and children eyes was 214.6±85.5 μm and 172.1±40.3 μm respectively. Mean subfoveal medium choroidal vessel thickness of adult eyes was significantly larger than children eyes ($P\leq$0.0001; Figure 2C). However, mean nasal and temporal medium choroidal thickness of children eyes was significantly larger than adult eyes (both $P\leq$0.0001).

Age-stratified Analysis of Choroidal Thickness Analysis was also completed with adult subjects stratified into younger adult subjects aged 18-50 years old inclusive and older adult subjects aged more than 50 years old (Figure 3). There were 46 younger adult subjects with mean age 36.05±8.2y. There were 34 older adult subjects with mean age 68.4±7.3y.

Mean SFCT of younger and older adults were 337.3±104.8 μm and 270.2±64.8 μm, respectively. Mean SFCT in younger adults was greater than in child eyes (P=0.001) but less than older adults (P=0.001). Nasal and temporal choroidal thickness of older adult eyes was greater than in both younger adults and child eyes (all P<0.05); temporal choroidal thickness in younger adults was also greater than children ($P\leq$ 0.01).

Mean subfoveal large choroidal vessel thickness of younger and older adults were 99.0±30.0 μm and 88.9±25.6 μm respectively. Mean subfoveal large choroidal vessel thickness of child eyes was significantly greater than older adults (P=0.004). There was no significant difference in large choroidal vessel thickness at either the nasal or temporal locations.

Mean subfoveal medium choroidal vessel thickness of younger and older adults were 237.2±97.4 μm and 181.1±53.9 μm, respectively. Mean subfoveal medium choroidal vessel thickness of younger adults was more than in child eye (P=0.004) but less than in older adults (P=0.003). Both nasal and temporal medium choroidal vessel thickness of child eyes was significantly greater than younger adults, which in itself was significantly greater than older adults (all P<0.05).

DISCUSSION

We report the difference in EDI-OCT derived choroidal thickness and large and medium choroidal vessel thickness between children and adult eyes. Our study suggests that SFCT of adult eyes is significantly larger than children eyes. It appeared that this variation was associated with a corresponding decrease in large choroidal vessel thickness and an increase in medium choroidal vessel thickness at the subfoveal location. However, this change at the subfoveal location was not reflected at the nasal and temporal loci measured in this study. In particular, nasal and temporal choroidal thickness (as well as medium choroidal vessel thickness) in children appeared to be significantly larger than in adults. Furthermore, there was no significant difference in large choroidal vessel thickness at either the nasal or temporal locations. This highlights the degree of topographic variation in these measurements and hence the requirement to define accurate measurement points within the macula

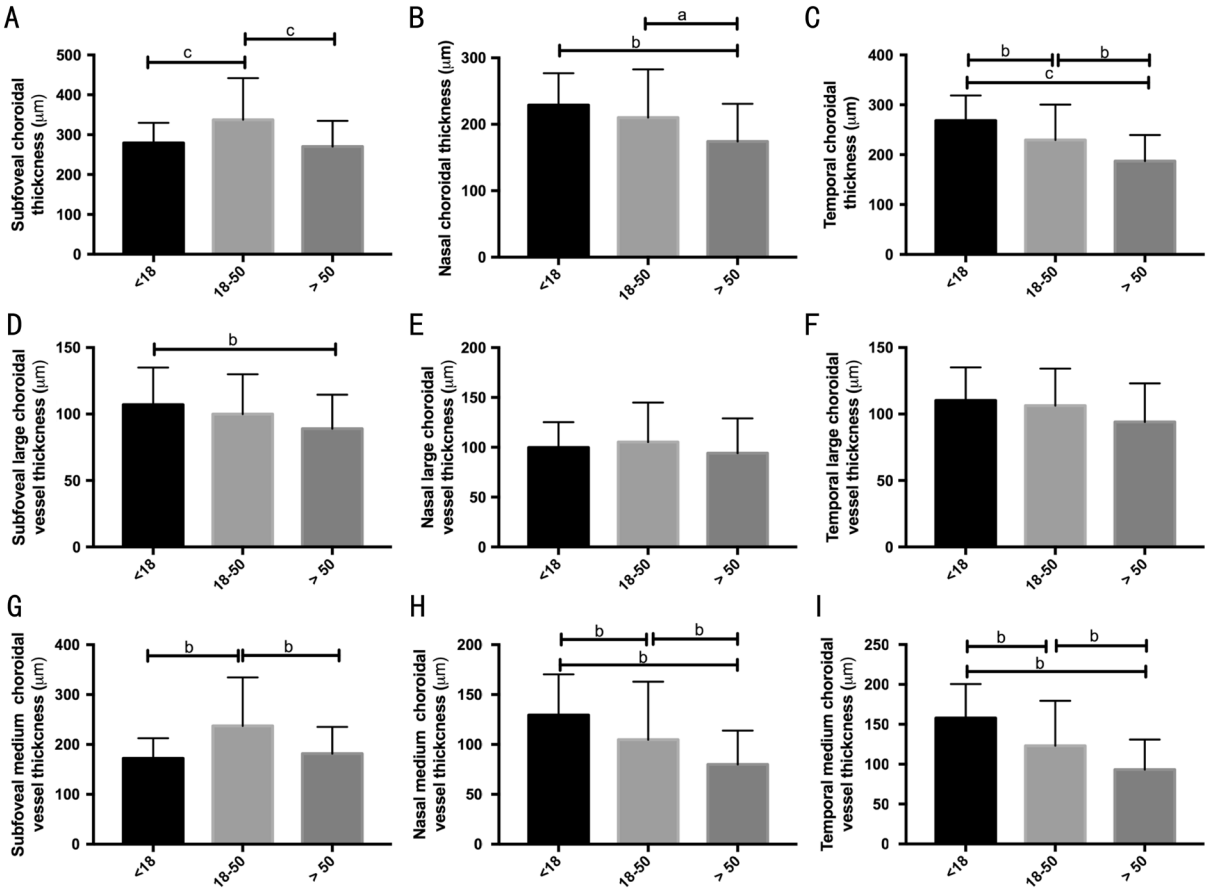

Figure 3 Age-stratified analysis of choroidal and choroidal vessel thickness EDI-OCT derived measurements of subfoveal choroidal thickness (A), nasal choroidal thickness (B) and temporal choroidal thickness (C) subfoveal large choroidal vessel thickness (D) nasal large choroidal vessel thickness (E) temporal large choroidal vessel thickness (F) subfoveal medium choroidal vessel thickness (G) nasal medium choroidal vessel thickness (H) temporal medium choroidal vessel thickness (I) in child (<18) and younger adult (18-50) and older adult (>50) eyes. ANOVA with post-hoc Tukey test: $^{a}P\leq0.05$; $^{b}P\leq0.01$; $^{c}P\leq0.001$; $^{d}P\leq0.0001$.

when comparing between individuals and between subsequent images.

The absolute choroidal thickness measurements found in our study are similar to OCT derived measurements previously reported in children[16-18]. However, whilst previous studies suggested that choroidal thickness is larger in children, our study suggests that choroidal thickness at the subfoveal location may be smaller[19]. This may be due to multiple factors affecting measurement accuracy including inter-observer variability; indeed, this variability has been noted to be greater at higher SFCT in CSC[20]. Furthermore, choroidal thickness measurements in CSC appear to significantly dependent on the type of OCT used[21]. It is important also to consider the increasing number of factors that have also been reported to affect choroidal thickness. Differences in choroidal thickness measurements may be accounted for by variation in refractive status, axial length, ethnicity and medical conditions (including obesity and hematological disease)[11-13]. Our study excluded subjects with refractive error of more than ±3 D spherical equivalent and confirmed that there was no difference in the refractive status between adult and pediatric populations. However, the variation in these other factors may certainly have influenced our analyses. It is interesting to note that age-stratified analysis of choroidal thickness suggested that although choroidal thickness was smaller in children in our younger adult population, it appeared to decrease again in our older adult subgroup. There was no significant difference between SFCT between children and older adult eyes. The relative number of younger and older adult eyes in this study may partly reflect the difference between our results and previous studies and could confirm that there is some thinning of the choroid in older adult populations.

Our results suggest that there is an alteration in choroidal vasculature with aging, specifically a decrease in large choroidal vessel thickness and increase in medium choroidal vessel thickness. Alteration in the relative amount of choroidal vasculature and stromal tissue has been investigated in several pathologies[9-10]. Reduction in the density of vascular networks with aging has also previously been described using OCT angiography. MRI analysis has also suggested that there is a reduction in choroidal blood flow velocity during aging[22]. These changes may account for the differences between child and adult eyes seen in our study. Interestingly, it appears that both large and medium choroidal vessel thickness appears to

be reduced in neovascular age related macular degeneration (nAMD)[23]. Indeed, our age-stratified analysis suggested that subfoveal large choroidal vessel thickness of older adults was greater than child eyes and subfoveal medium choroidal vessel thickness in older adults was greater than younger adults. Perhaps, underling changes in choroidal vascularity associated with aging appear before pathological changes described in AMD[23]. Indeed, alteration in choroidal physiology with reduced choroidal bood flow has been noted in laser flowmetry studies of patients with nAMD[24]. Analysis of medium choroidal vessel thickness may be useful in our understanding of the pathophysiology of the pachychoroid phenotype[25]. The pachychoroid spectrum disorders are associated with a very large outer choroid (large vessel) and thinned medium vessel and include CSC and polypoidal choroidal vasculopathy. Our results demonstrate the alterations of choroidal layers in normal ageing, and this may help to understand the pachychoroid condition.

The strengths of this study include the analysis of both adult and child eyes using the same protocol (including type of OCT and method of choroidal layer thickness measurement) for a range of choroidal parameters at several locations. Limitations of this study include the possibility of diurnal variation in choroidal thickness affecting our results[26]. Our results did not include superior and inferior macular quadrants; given that temporal and nasal findings did not necessarily reflect subfoveal findings, it may be important to describe thickness patters in other extrafoveal loci. Further analysis of choroidal thickness variation between adult and children is needed; possible variation due to other factors (including body mass index, blood pressure, haematological conditions) require evaluation to delineate the effects of age on choroidal thickness parameters more precisely[14-15]. It would also be useful to extend this study further with a larger population of normal individuals across a range of different ethnicities.

In summary, we report that EDI-OCT derived choroidal thickness measurements in children are greater than in adult eyes. This change in choroidal thickness appeared to be associated with a reduction in subfoveal large choroidal vessel thickness and an increase in medium choroidal thickness. These results have implications for our understanding of aging changes in the choroid and assessment of chorioretinal disease in children.

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Conflicts of Interest: Hanumunthadu D, None; **Ruiz-Medrano J,** None; **Dumpala S,** None; **Jabeen A,** None; **Jabeen A,** None; **Goud A,** None; **Ruiz-Moreno J,** None; **Chhablani J,** None.

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