·Clinical Research·

# Comparison of central macular thickness between two spectral-domain optical coherence tomography in elderly non-mydriatic eyes

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## Abstract

• AIM: To compare central macular thickness (CMT) measurements obtained by two spectral-domain optical coherence tomography (SD-OCT) exams, and to evaluate measurement reproducibility and agreement between these two exams, and to investigate the relationship between CMT and possible influencing factors such as age, sex, eye (OD/OS), and operators in elderly non-mydriatic eyes.

• METHODS: Seventy-two normal subjects were included. Every subject underwent CMT measurement twice using one of two SD-OCT (OSE-2000, Moptim, Shenzhen, China & 3-D OCT-1000, Topcon, Tokyo, Japan) instruments respectively where we randomly chose one eye in each patient for the test; these exams were performed by two operators over an hour period with a brief rest between sessions. Comparison of the OSE-2000 and 3-D OCT-1000 CMT measurements was based on paired-*t* test. The mean difference between the CMT measurements was calculated. General linear model analyzed the relationships among eye (OD/OS), operator, sex, and CMT values using age as co-variant. All tests were considered statistically significant at $P<0.05$. The main outcome measures included CMT.

• RESULTS: When evaluated with general linear model analysis, CMT measurements were found to have high reproducibility across the two instruments between the two operators for the OSE-2000 single line scan and 3-D OCT-1000 macular scans ($P=0.731$; $P=0.443$). There was statistically significant difference in CMT values between the two instruments ($P<0.001$) and the mean difference was -46.83μm at 95% confidence limits (-49.15,-44.51). Age was positively correlated with CMT (beta coefficient =0.516, $P=0.001$; beta coefficient=0.453, $P=0.009$) and sex was correlated with CMT from the OSE-2000 ($P=0.021$) but not with the 3-D OCT-1000 ($P=0.056$). According to the actual thickness measurements, the CMT of the male was thicker than the female's but there was no statistical difference. There was interaction between sex and eye in OSE-2000 and not in 3-D OCT-1000 ($P=0.02$; $P=0.374$). No significant correlation was found between CMT and the influencing factor of eye in both of the instruments($P=0.884$; $P=0.492$).

• CONCLUSION: Reproducibility of CMT measurement using the two SD-OCTs is excellent in normal eyes according to the operator factor analysis. OSE-2000 has a different posterior retinal boundary of CMT measurement, which results in the CMT value differences, compared with the 3-D OCT-1000. Age is positively correlated with CMT measurement while sex is correlated with CMT in the OSE-2000 but not in the 3-D OCT-1000 and eye (OD/OS) had no correlation with CMT values. Mydriatic drops may not be necessary for CMT measurement using high scan rate SD-OCT in normal eyes in dark room.

• KEYWORDS:central macular thickness; spectral-domain optical coherence tomography; non-mydriatic eyes

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## INTRODUCTION

Optical coherence tomography (OCT), which was introduced in 1991, is probably one of the most amazing developments in ophthalmic imaging technology[1-3]. The first time-domain optical coherence tomography (TD-OCT) machine from Carl Zeiss had an axial resolution of about 15μm. With the advent of a new OCT system, the SD-OCT, the axial resolution of 5μm is close to being a clinical reality. An accurate, reliable, and repeatable assessment of the macular zone, especially central macular thickness (CMT) alterations, is vital to the diagnosis of macular diseases in patient follow-ups and clinical trials.

**Table 1 The macular scan protocol of OSE-2000 and 3-D OCT-1000**

| | San protocol | Scan length | Scan area | CMT boundary |
|---|---|---|---|---|
| OSE-2000 | Single line | 6mm | Macular region | ILM-IS/OS |
| 3D OCT-1000 | 3D type | 6×6mm | Macular region | ILM-RPE |

ILM: Internal limiting membrane; IS/OS: Photoreceptor inner/outer segment junction; RPE: Retinal pigment epithelium; CMT: Central macular thickness.

The OCT has an excellent ability to detect the inner and outer retinal boundaries and then to calculate the thickness between any two layers using software from the acquired cross-sectional retinal structural images. The reproducibility and reliability of CMT measurements with the Topcon 3-D OCT-1000 has been reported in several studies [4,5]. It was therefore of interest to test the new OSE-2000 OCT instrument to see if it gave the same CMT values, reproducibility, and reliability as the Topcon 3-D OCT-1000, to investigate the possible reasons for the fluctuation in CMT values, and to investigate the relationship between central macular thickness and influencing factors such as age, sex, eye (OD/OS), and operators in the two different instruments.

## MATERIALS AND METHODS

**Subjects** One eye from each of the 72 subjects (40 males and 32 females) for a total of 72 eyes was included in the study. All subjects had a best corrected visual acuity (BCVA) of at least 20/40, spherical error between +2.5 and -6.0 D, and no clinical evidence of any ocular or systemic disease. Volunteers with clinical evidence of hypertensive disease, diabetes, neurological diseases, macular diseases, or previous refractive surgery were excluded. For each eye in the study, two CMT measurements were obtained from both instruments randomly performed by two experienced technicians over an hour; each patient got a brief rest between sessions in the dark room. No mydriatic drops were used during the entire procedure. The study was conducted in accordance with the ethical standards of and approved by the Clinical Research Ethics Committee in China.

**OSE-2000 and 3-D OCT-1000 Imaging** OCT technology has improved greatly from the conventional TD-OCT to the SD-OCT. SD-OCT provides increased resolution and scanning speed by recording the interferometric information with a Fourier-domain spectrometric method instead of adjusting the position of a reference mirror [6,7]. The imaging speed is 60 times faster and the resolution is almost 5 times higher than the conventional TD-OCT. The OSE-2000 SD-OCT system, which was firstly invented through the cooperation of the Moptim Company and Tsinghua University in China, has been approved in 2010 by the State Food and Drug Administration (SFDA) for clinical use in China. It has a field angle of 29°×23° with charge-coupled device (CCD) imaging included. The horizontal resolution is about 15μm and the depth resolution is up to 5μm. The light source of the system uses super luminescent diodes with a wavelength of 840nm similar to the Topcon 3-D OCT-1000 system. The scan rate is 20 000 A-scan per second, which is a little lower than the Topcon's rate of 27 000 A-scan per second. The Topcon OCT system has a field angle of 45° with color fundus imaging; the resolution of horizontal and depth is about 20μm and 5μm respectively. All of the images in this study were captured by two experienced and trained technicians. The image quality score was more than 6 for the OSE-2000 and more than 65 for the 3-D OCT-1000.

**Scan Protocol** Auto-measurement values after the macular single line scans were recorded for the OSE-2000. Using the color fundus image, we chose three consecutive cross-sectional OCT images, corresponding to the foveolar area, to do the caliper measurements. We then selected the minimum measurement of the three as the CMT of record for the 3-D OCT-1000(Table 1).

**Statistical Analysis** Statistical analysis were performed with commercial software (SPSS 13.0; SPSS Inc). Comparison of the OSE-2000 and 3-D OCT-1000 CMT measurements was based on a paired $t$-test. The mean difference between CMT measurements was calculated. The General Linear Model analyzes the relationship between eye (OD/OS), operator, sex, and CMT values using age as covariant. All tests were considered statistically significant at $P<0.05$.

## RESULTS

The mean BCVA of these eyes was 0.63°z±0.11 (range, 20/40-20/25) and the mean age was (67.5±7.6) years (range, 50-85). The average refractive error in spherical equivalent (SE) was (-0.48±2.04)Ds (range, -6-2.5). Using general linear model analysis, the central macular thickness measurements were found to have high reproducibility from the OSE-2000 single line scans and 3-D OCT-1000 macular scans respectively ($P=0.731$, $P=0.443$; Figure 1); these scans were given by two different operators. The mean central macular thickness was (139.53±16.37)μm and (186.37±18.01)μm for the OSE-2000 and 3-D OCT-1000 respectively. The OSE-2000 CMT measurement values were significantly thinner than the ones from the 3-D OCT-1000 ($P<0.001$) and the mean difference was -46.83μm at 95% confidence limits (-49.15,-44.51; Table 2, Figure 2). Age was positively correlated with central macular thickness (beta coefficient=0.516, $P=0.001$; beta coefficient=0.453, $P=0.009$) and sex was correlated with the central macular thickness of OSE-2000 measurements ($P=0.021$) but not in the 3-D OCT-1000 results ($P=0.056$). The central macular

**Table 2** Comparison of CMT measured by OSE-2000 and 3D OCT-1000

| | OSE-2000 (mean±SD) | 3D OCT-1000 (mean±SD) | [1]*P* | Mean difference (OSE-2000 and 3D OCT-1000) | 95% confidence limits |
|---|---|---|---|---|---|
| CMT | 139.53±16.37 | 186.37±18.01 | <0.001 | -46.83 | (-49.15,-44.51) |

[1]Paired *t*-test.

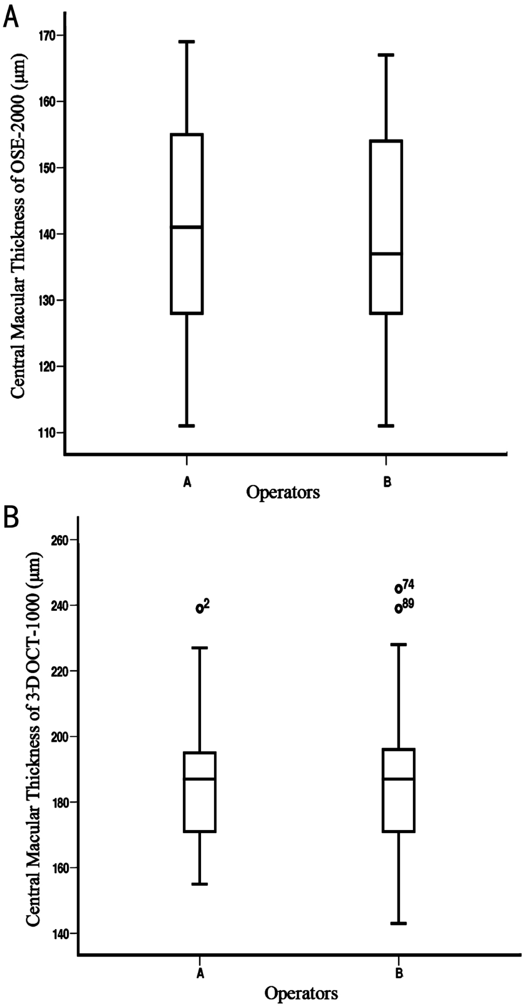


**Figure 1 Box plots of the correlation between CMT and different operators, there is no significant correlation between the CMT and different operators in OSE-2000 ($P$=0.731) and 3-D OCT-1000 ($P$=0.443) respectively** A: OSE-2000 B: 3-D OCT-1000.

thickness of the male participants is thicker than those of the females although there was no statistical difference between the two (Figure 3). There was interaction between sex and eye in the OSE-2000 measurements but not in the 3-D OCT-1000 ($P$=0.02, $P$=0.374; Table 3). The interaction between sex and eye in the OSE-2000 shows that the CMT values of OS in males and females are (138.76±2.676)μm and (138.764±2.478)μm respectively. There is no significant difference between male and female OS measurements; however, the CMT value of the male volunteers (144.665±2.28)μm is higher than the female's (132.083±3.153)μm in OD (Figure 4). No significant correlation was found between the CMT and the influencing factor of eye with both of the instruments ($P$=0.884, $P$=0.492).

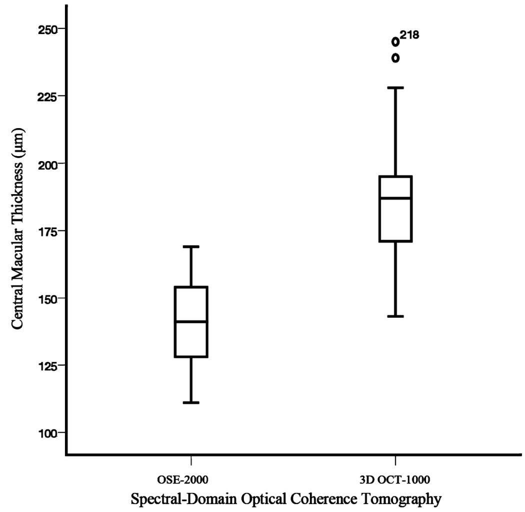


**Figure 2 Box plots of the CMTs determined by using different SD-OCTs, the macular thickness is significantly thinner in OSE-2000 than in 3-D OCT-1000 ($P$<0.001).**

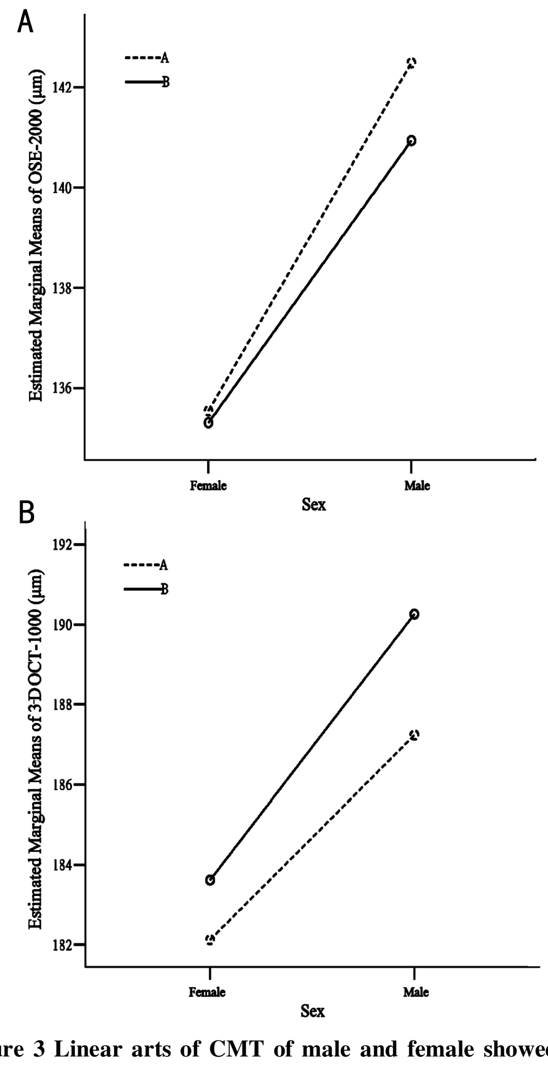


**Figure 3 Linear arts of CMT of male and female showed that the CMT of male is thicker than the female in both of them** A: OSE-2000; B: 3-D OCT-1000.

**Table 3 General linear model analysis of influencing factor for OSE-2000 and 3D OCT-1000**

| | OSE-2000 | | 3D OCT-1000 | |
|---|---|---|---|---|
| | F | *P* | F | *P* |
| Sex | 5.441 | 0.021 | 3.707 | 0.056 |
| Operator | 0.119 | 0.731 | 0.592 | 0.443 |
| Age | 11.805 | 0.001 | 7.106 | 0.009 |
| Eye | 0.021 | 0.884 | 0.475 | 0.492 |
| [1]Sex Eye | 5.559 | 0.020 | 0.797 | 0.374 |
| [1]Eye Operator | 0.016 | 0.901 | 0.151 | 0.698 |
| [1]Sex Operator | 0.062 | 0.804 | 0.066 | 0.798 |

[1]General Linear Model for interaction analysis.

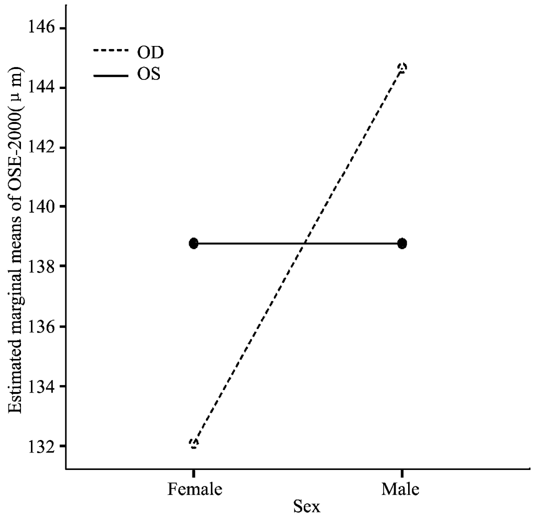


**Figure 4 Linear art of the interaction between sex and eye of CMT of OSE-2000 (*P*=0.02)** .

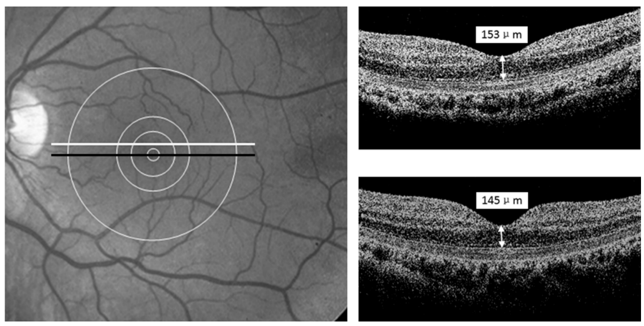


**Figure 5 The schematic diagram shows that capture moment of scan line in central macula may be in foveola (black line, corresponding to the lower OCT image of right side, 145μm) or in other places of fovea (white line, corresponding to the upper OCT image of right side, 153μm) due to the tiny unstable fixation and the OCT cross-sectional image of macula curvature remains there, but shows different CMT values.**

## DISCUSSION

CMT measurements with the time-domain OCT have been demonstrated to be repeatable and accurate in previous studies[8,9].

**Reproducibility of OSE-2000 and 3-D OCT-1000** In our study, different statistical analysis methods were used to analyze the reproducibility of the instruments than previous studies which used intraclass correlation coefficients [10, 11]. In the results of this study, the statistical analysis also shows that the different operators have no significant correlation with CMT values and demonstrates that good reproducibility with the OSE-2000 and 3-D OCT-1000 ($P$ =0.731; $P$ = 0.443) exists. In other words, the OSE-2000 has as good reproducibility and stability in CMT measurements as the 3-D OCT-1000 does.

**No mydriatic drops** The SD-OCT has a higher axial resolution and lower minimum pupil diameter requirement (2-3mm), which can be satisfied by closing the eyes for three minutes in a dark room before taking images according to Li *et al* [12] study. According to optical theory, the ocular aberrations resulting from large pupil diameters limit the minimum focus spot size on the retina and limit transverse resolution for retinal imaging [13]. So, not using mydriatic drops as in the Leung *et al* [14] study may not affect the CMT measurement accuracy if the pupil size meets the SD-OCT scanning requirement.

**Different posterior retinal boundary** No international unified standard about the CMT measurement boundary exists in clinical care; there have been previous studies that have researched this phenomenon [15-17]. In this study, the mean central macular thickness was 139.53±16.37μm and (186.37±18.01)μm for the OSE-2000 and 3-D OCT-1000 respectively. The OSE-2000 CMT measurement value was thinner than the 3-D OCT-1000 ($P$<0.001) and the mean difference was -46.83μm with a 95% confidence limit (-49.15, -44.51). The poor agreement in CMT measurements between the two instruments results from the different posterior retinal measurement boundary. In the OSE-2000, the posterior retinal boundary is the photoreceptor inner segment/outer segment (IS/OS) but in the 3-D OCT-1000, the retinal pigment epithelium (RPE) is set as the posterior boundary [18]. So the two boundaries used by the two instruments, IS/OS and RPE, have photoreceptor outer segment, microvilli in between them; the thickness of these structures is 46.83μm in this study The mean CMT values measured by OSE-2000 are thinner than the researchers found in the Stratus OCT study by Leung *et al* [14] even if they have the same posterior retinal boundary. The possible reasons for this discrepancy include the older age of the study subjects, overall average macular thickness decreases significantly as age increases as Song *et al* [19] and Eriksson *et al* [20] described, and the different races of the populations. The mean CMT obtained by the 3-D OCT-1000 is thinner than in a previous study[14] which recorded the auto-measured average foveal thickness values, not the minimum one.

**Possible Reasons for Fluctuation of CMT Values** There are some possible reasons to explain the high variability between CMT measurements just as the standard deviation shows between the two OCT instruments. First, small amounts of unstable fixation exist in normal eyes. [21,22] Patients need to focus on the default fixation point to put the macula into the center of the window when doing the OCT macular region scan; the study of fixation stability measurement using a microperimeter [22] appears to demonstrate that fixation is not always stable even for normal eyes. In other words, we can't ensure that the OCT capture moment and the scan line locations are not all in the foveola and not of other places in the fovea, even if the technique of eye tracking and 3-D-scan model is used (Figure 5). Second, the intervals between lines exist in 3-D scan model. For a 3-D scan model in the macular region, the typical method is performing 128 or more single line slides in either the horizontal or vertical direction in the 6mm× 6mm macular region. Then the computer reconstructs the three-dimensional structure according to the signal data collected in every single line scan. This type of scan protocol cannot exactly scan everywhere in the cube due to line interval, that also results in the difference in CMT measurements, even for the same eye at different times. Third, the 3-D OCT-1000 does not utilize real-time scans with the color and the cross-sectional images. The color fundus image was taken after the OCT cross-sectional scan was finished to avoid the irritation of the pupil by the flashlight--especially in non-mydriatic conditions. Therefore, the fundus image and the OCT image do not achieve real one-to-one correspondence. Last but not least, eye tracking could achieve more precise repeatability. However, it would not be perfect until we settle the above-mentioned second aspect problem.

**Influencing Factors** Age was positively correlated with central macular thickness for the OSE-2000 and 3-D OCT-1000 (beta coefficient=0.516, $P$=0.001;beta coefficient =0.453, $P$=0.009). This result is in accordance with the Duan *et al*[23] and Kashani *et al*[24] studies but different than the Wong *et al* [25], Ooto *et al* [26],and Zhang *et al* [27] conclusions. Sex was correlated with the central macular thickness in the OSE-2000 results ($P$=0.021) and the value of the male was thicker than the female's. The results were in accordance with previous studies[24,25,27] but opposite to the Rao *et al* [28] study conclusion. There was no relationship between sex and CMT of the 3-D OCT-1000 ($P$=0.056), which is consistent with the Rao *et al* [28] study. The interaction of sex and eye in the central macular thickness results of the OSE-2000 is a new finding which is different from Wexler *et al* [29] The different results from previous studies [23-29] about age, sex, and the interaction between sex and eye may due to the different age groups and races in each study. Eye (OD/OS) has no significant correlation with CMT measurements in this study ($P$=0.084; $P$=0.492) similar to the Asefzadeh *et al*[30] study. It means that OD or OS will not influence the values of CMT but the interaction between sex and eye should still be considered in that situation. The operator has no significant correlation with CMT measurements in this study ($P$=0.731), as was seen in previous studies about the Stratus OCT [31] and Topcon OCT [32]. In other words, it reveals that both the OSE-2000 and 3-D OCT-1000 can provide repeatable and reliable values for CMT measurement. In all, the correlation between sex, age, eye (OD/OS), and macular thickness has not demonstrated any unified conclusions in previous research. [1,15,23,33,34] Further studies with larger sample size are needed to provide more useful information regarding differences among age, sex, eye (OD/OS), and central macular thickness, especially for the interaction study.

In summary, although there is difference in CMT values between the OSE-2000 and 3-D OCT-1000, both of them are reproducible and reliable for CMT measurements. International unified standards about the clear location of the retinal posterior boundary for CMT measurement could be established for better comparison of different SD-OCT instruments by further research. Finally, the OSE-2000 and 3-D OCT-1000 are reproducible and reliable for measuring macular thickness and these variables such as age, sex and interaction between sex and eye should be considered while evaluating the central macular thickness.

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