# Choroidal Thickness in Diabetic Patients Without Diabetic Retinopathy: A Meta-analysis

HIROAKI ENDO, SATORU KASE, MICHIYUKI SAITO, MASAHIKO YOKOI, MITSUO TAKAHASHI, SUSUMU ISHIDA, AND MANABU KASE

• PURPOSE: To evaluate the relationship between diabetic eyes without diabetic retinopathy and healthy eyes in subfoveal choroidal thickness.
• DESIGN: Systematic review and meta-analysis.
• METHODS: An independent retrospective or prospective clinical study comparing diabetic eyes without diabetic retinopathy and healthy control eyes in the subfoveal choroidal thickness was selected. This study compiled data from publications in PubMed and Web of Science between January 1, 2008, and November 15, 2019. Heterogeneity was statistically quantified by I2 statistics, and meta-analysis was performed using a random-effects model.
• RESULTS: Seventeen related studies were identified, including a total of 4,213 eyes, which consisted of 1,197 diabetic eyes without diabetic retinopathy and 3,016 healthy eyes. Meta-analysis clearly showed that the subfoveal choroidal thickness of diabetic eyes without retinopathy was significantly thinner than that of healthy control eyes (weighted mean difference = −14.34 μm; 95% confidence interval: −24.37 to −4.32 μm; $P < .005$). Similar results were obtained in sub-analysis based on the adjustment of the axial length.
• CONCLUSIONS: This study suggests that the subfoveal choroidal thickness was thin in diabetic eyes without retinopathy compared to healthy eyes. Subfoveal choroidal thickness might be an important parameter for the development of diabetic retinopathy in diabetic eyes without retinopathy. (Am J Ophthalmol 2020;218:68–77. © 2020 Elsevier Inc. All rights reserved.)

DIABETIC RETINOPATHY (DR) IS ONE OF THE MAJOR causes of visual impairment in the working-age population worldwide.[1] The etiology of DR is primarily owing to dysregulation of the retinal microvascular systems, including disruption of the blood-retinal barrier.[2] The choroid takes part in the retinal function by continuous perfusion into the outer retina, which plays critical roles in thermoregulation of the retina, maintenance of the anatomic position of the retina, removal of residues, and secretion of growth factors.[3] Previous histologic studies using cadaver diabetic eyes demonstrated several choroidal vascular abnormalities such as choriocapillaris obstruction, vascular degeneration, and choroidal neovascularization.[4–6] In fact, recent evidence also has established the presence of diabetic choroidopathy.[7–9]

Optical coherence tomography (OCT) is a noninvasive technique commonly used for fundus imaging, which allows ophthalmologists to evaluate morphologic features of the retina. Newer OCT technologies facilitated analyses with higher resolution, deeper tissue penetration, and faster acquisition rates. The advent of enhanced depth imaging (EDI) technology[10] and swept-source OCT (SSOCT)[11] has enabled to obtain better visualization of the choroid in vivo and quantitative assessment of choroidal thickness.

The previous OCT-based choroidal evaluations demonstrated a significant change in choroidal thickness in diabetic eyes without DR,[12–14] but the others could not prove the facts.[15] In recent years, we have reported the alteration of choroidal structures in diabetic eyes without DR, which correlated with the duration of diabetes.[16] Despite an increased number of literatures on this topic, to our knowledge there is no meta-analysis that focuses on the choroidal thickness in diabetic eyes without DR and healthy control eyes. Therefore, meta-analysis may be able to provide reliable data to solve this problem.

The purpose of this study was to perform a meta-analysis and to systematically evaluate the measurement of choroidal thickness using OCT in diabetic eyes with no DR (NDR) and healthy control eyes.

## METHODS

• LITERATURE SEARCHES: This meta-analysis was performed according to the predefined protocols described below. We searched PubMed and Web of Science using search items including "choroidal thickness," "diabetes mellitus," "diabetic retinopathy," "diabetic choroidopathy," and "optical coherence tomography." A manual search was performed by checking the reference list of

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From the Department of Ophthalmology, Teine Keijinkai Hospital, Sapporo, Japan (H.E., M.T., M.K.); Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan (S.K., M.S., S.I.); and Teine Yokoi Eye Clinic, Sapporo, Japan (M.Y.).

Inquiries to Satoru Kase, Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, N15 W7, Kita-ku, Sapporo 060-8638, Japan; e-mail: kaseron@med.hokudai.ac.jp



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original reports and review articles to identify studies that were not yet included in the computerized database. The language in the process was limited to English, and studies examining human subjects were included in the search. Literature selection was searched in a 2-step process. The first step was to screen the literature from title and abstract. In the second step, the full text of the literature was scrutinized and those that met the eligibility criteria were selected. Data extraction and quantitative evaluation were performed by 2 investigators, and if the results did not match, the eventual agreement was reached through discussion. The final search was conducted on November 15, 2019. The institutional review board in Teine Keijinkai Hospital approved the study protocol of this clinical research (IRB number: 3-020014-00).

• **INCLUSION AND EXCLUSION CRITERIA:** In this meta-analysis, we included studies according to the following inclusion criteria: (1) independent retrospective or prospective studies; (2) researches using spectral-domain OCT (SDOCT) with EDI technology and SSOCT; (3) studies evaluating the choroidal thickness in type 1 or type 2 diabetes mellitus (DM) patients without DR; (4) studies that include the results of subfoveal choroidal thickness (SCT) measurements; (5) studies reporting the thickness with means and standard deviations presented as μm units, or in which it was possible to measure them from the data presented in the studies by our own calculation.

Exclusion criteria included the following: (1) studies lacking healthy control eyes; (2) abstracts from conferences, case reports, comments, or reviews; (3) studies lacking possible data searched; or (4) duplicated articles. If some studies were carried out using the same populations, the authors selected the most recent study or the most complete study. The screening process was performed separately by 2 reviewers, and disagreements were resolved by discussion and consent.

• **DATA EXTRACTION:** Two reviewers extracted the required information from eligible studies using standardized forms. The extracted data included the following: (1) first author, (2) publication year, (3) study design, (4) origin of study, (5) type of OCT instrument, (6) sample size, (7) age, (8) axial length, (9) DM type, (10) duration of diabetes, (11) serum hemoglobin A1c (HbA1c), and (12) choroidal thickness. Differences in results obtained by the reviewers were resolved by discussion.

• **QUALITY ASSESSMENT:** First, the methodology quality of the included studies was evaluated based on the Cochrane Handbook for Systematic Reviews of Interventions by 2 reviewers. Next, the quality of case-control studies in meta-analysis was graded based on the Newcastle-Ottawa Scale (NOS) system.[17] The NOS system is usually used for nonrandomized studies and can include cohort studies as well as case-control studies. The NOS system evaluated 3 dimensions (selection, comparability, and exposure), with a maximum score being 4, 2, and 3 for selection, comparability, and exposure, respectively. Then, a 9-step NOS score (range, 0-9) was determined for evaluation. A study was defined as high quality if it scored 7 or more. If the NOS score was 4-6, or less than 4, the study was defined as medium or low quality, respectively. Studies of more than 4 points were considered a sufficient quality, which were included and processed into the final analysis.

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using Cochrane Review Manager 5.3, and significance levels were set at $P < .05$, which were evaluated as statistically significant. This study calculated the weighted mean difference (WMD) between diabetic eyes and healthy control eyes, and 95% confidence interval (CI) for the choroidal thickness. We assessed the heterogeneity between studies using the $I^2$ statistic. Values of 25%, 25%-49%, 50%-74%, and over 75% are considered nonuniform, low, medium, and high nonuniformity, respectively. In the absence of heterogeneity ($I^2 < 50\%$), a fixed-effects model was used. Otherwise, a random-effects model was applied to integrate the data. Potential publication bias was assessed using funnel plots, and Begg's test and Egger's test were applied for quantification.

## RESULTS

• **SEARCH AND SELECTION OF STUDIES:** Figure 1 shows the details of the research selection process in this study. The initial search strategy identified 274 articles, of which 121 reports were removed because of duplicate studies. After the title and summary screening, 125 reports were excluded because they were obviously irrelevant. Then the eligibility of 28 full-text articles was further evaluated. Finally, 17 studies met inclusion criteria in this study and were submitted to the meta-analysis.[12–14,16,18–30]

• **CHARACTERISTICS AND QUALITY OF STUDIES:** The Table summarizes the studies included in the meta-analysis. Of the 17 studies, 9 were conducted in Asia, 7 in Europe, and 1 in North America. The mean age ranged from 44.5 to 68.6 years. All studies enrolled age-matched subjects with DM patients and healthy controls, and 8 studies out of 17 further enrolled axial length–matched subjects. Thirteen studies employed the SDOCT device using EDI technology to obtain data of SCT. Seven and 5 studies used Spectralis (Heidelberg Engineering, Heidelberg, Germany), and Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, California, USA), respectively. One study used 3D OCT-1000 (Topcon Corporation, Tokyo, Japan). In addition, SSOCT DRI OCT Triton (Topcon Corporation, Tokyo, Japan) was employed in 4 studies. All studies had

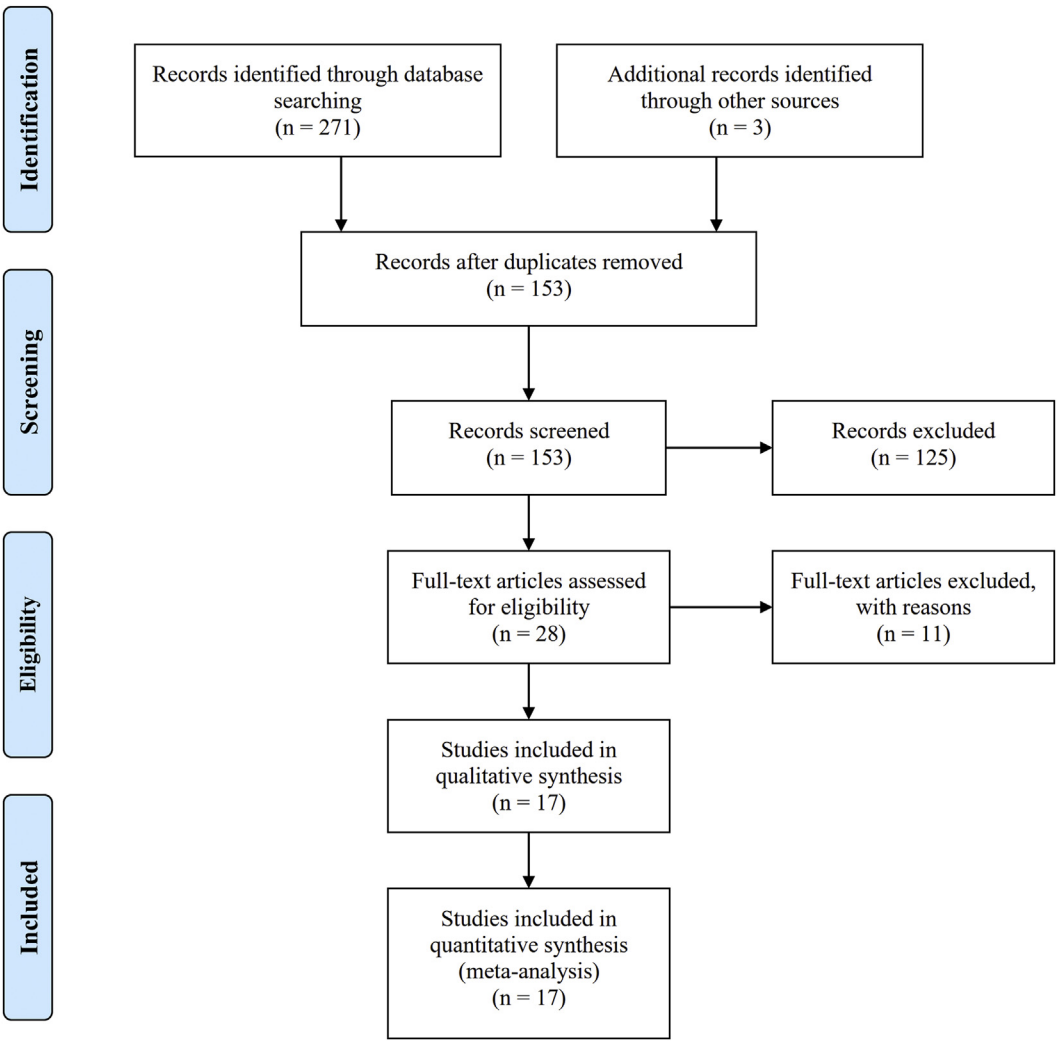


**FIGURE 1. PRISMA flow diagram of the literature search process. The initial search strategy identified 274 articles, in which 121 reports were removed because of duplicate studies. After the title and summary screening, 125 reports were excluded because they were obviously irrelevant. Then the eligibility of 28 full-text articles was further evaluated. Finally, 17 studies met inclusion criteria in this study, which were submitted to the meta-analysis.**

≥4 in the NOS score with an average of 6.1, indicating generally good methodological quality.

• **META-ANALYSIS:** *Changes in Subfoveal Choroidal Thickness*. Figure 2 shows the meta-analysis of SCT between NDR eyes and healthy control eyes. All studies used the built-in caliper tool manually as a measurement method. Because heterogeneity ($I^2$ = 84%) was substantial, a random-effects model was used to present the data. The results showed that SCT of NDR eyes was significantly thinner than healthy control eyes (WMD = −14.34 μm; 95% CI: −24.37 to −4.32; $P < .005$).

In contrast, SCT showed significantly thicker in NDR than healthy eyes in 1 study.[14] The other 3 studies revealed thickened choroid in NDR, but they were not significantly different.[20,22,23] In fact, the axial length was not adjusted in 3 of those 4 studies (Figure 3). The origin of 3 of the studies was Europe, and 1 study was from North America; however, Asian populations were not included. For the countries surveyed, data on race were not given in the dissertation, so there is insufficient information to consider ethnicity.

*Sub-analysis by Adjustment of Axial Length*. As shown in the Table, whether the axial length is adjusted or not causes the nonuniformity, which might be a serious limitation of the analysis. Previous reports have shown that SCT decreases significantly with increasing axial length.[31] Therefore, SCT needs to be evaluated under strict control of the axial length. To resolve this problem, a sub-analysis by adjusting the axial length was performed. In the studies after the axial length was

**TABLE.** Characteristics of the Included Studies

| Study | Author | Year of Publication | Country | OCT | Number of Eyes | | Age (Years) | | Axial Length (mm) | | Type of DM (1/2) | Duration of DM (Years) | HbA1c (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | DM | Control | DM | Control | DM | Control | | | |
| 1 | Querques | 2012 | Italy | Spectralis | 21 | 21 | 65 | 65 | – | – | 2 | – | – |
| 2 | Lee | 2013 | Korea | Spectralis | 59 | 48 | 57.5 | 55.8 | 24.5 | 24.5 | – | 5 | 7.4 |
| 3 | Kim | 2013 | Korea | Spectralis | 32 | 32 | 62.0 | 59.8 | – | – | 2 | 8.6 | 6.5 |
| 4 | Xu | 2013 | China | Spectralis | 223 | 1795 | 66.0[d] | 65.9 | 23.10[d] | 23.40 | – | – | – |
| 5 | Sudhalkar | 2015 | India | Cirrus | 74 | 197 | 53.00 | 41.48 | – | – | – | 9.45 | – |
| 6 | Tan | 2016 | Singapore | 3D OCT | 25 | 38 | 68.55[c] | 70.00 | 23.77 [c] | 23.75 | – | – | – |
| 7 | Shen | 2017 | India | Cirrus | 49 | 26 | 68.0 | 65.1 | – | – | 2 | 10.43 | 6.48 |
| 8 | Gupta | 2017 | Singapore | Spectralis | 100 | 273 | 61.85 | 60.10 | 23.38 | 23.38 | – | 14.71 | 7.49 |
| 9 | Kim | 2018 | Korea | Triton | 30 | 45 | 57.5 | 57.47 | – | – | 2 | 6.97 | 6.60 |
| 10 | Ambiya | 2018 | India | Cirrus | 100 | 100 | 59.73 | 57.52 | – | – | 1, 2 | 7.47 | – |
| 11 | Horváth | 2018 | Hungary | Triton | 17 | 46 | 58.75[b] | 59.80 | – | – | 1, 2 | 17.73 | 7.64 |
| 12 | Abadia | 2018 | Spain | Triton | 49 | 71 | 66.2 | 68.0 | 23.7 | 23.9 | 2 | 13.3 | 7.4 |
| 13 | Laíns | 2018 | USA | Triton | 27 | 50 | 68.3 | 64.3 | – | – | – | 14.8 | 6.38 |
| 14 | Tavares Ferreira | 2018 | Portugal | Spectralis | 125 | 50 | 66.9 | 67.18 | 23.11 | 22.51 | 2 | 5[e] | 6.4[e] |
| 15 | Wang | 2019 | China | Spectralis | 22 | 38 | 61.77 | 63.42 | 23.86 | 24.10 | – | 5.23 | 7.54 |
| 16 | Endo | 2019 | Japan | Cirrus | 105 | 117 | 61.2 | 62.6 | 23.84 | 23.87 | 2 | 8.6 | 8.1 |
| 17 | Carbonell | 2019 | Spain | Cirrus | 139 | 69 | 44.5[a] | 45.1 | – | – | 1 | 20.6 | 7.60 |

DM = diabetes mellitus; OCT = optical coherence tomography.
[a]Includes no diabetic retinopathy (DR), mild nonproliferative DR (NPDR), and advanced DR.
[b]Includes no DR, NPDR, and proliferative DR.
[c]Includes no DR and DR.
[d]Includes no DR, mild NPDR, and moderate NPDR.
[e]Shows median.

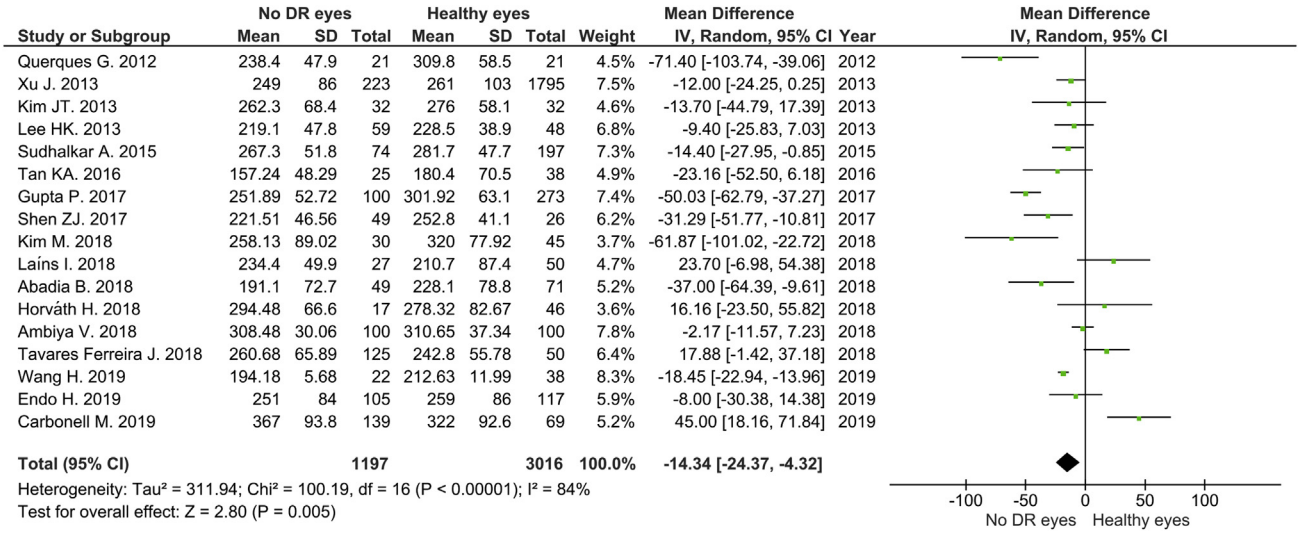


**FIGURE 2. Forest plot to evaluate meta-analysis of subfoveal choroidal thickness (SCT) between No DR eyes and healthy control eyes. The results showed that SCT of No DR eyes was significantly thinner than healthy control eyes. CI = confidence interval; DR = diabetic retinopathy; IV = inverse variance; SD = standard deviation.**

adjusted, SCT of NDR eyes was significantly thinner than healthy control eyes (WMD = −17.48 μm; 95% CI: −29.97 to −5.00; $P < .006$) (Figure 3A). However, there was no significant difference in the studies unless the axial length was adjusted (WMD = −11.35 μm; 95% CI: −29.82 to 7.12; $P < .23$) (Figure 3B).

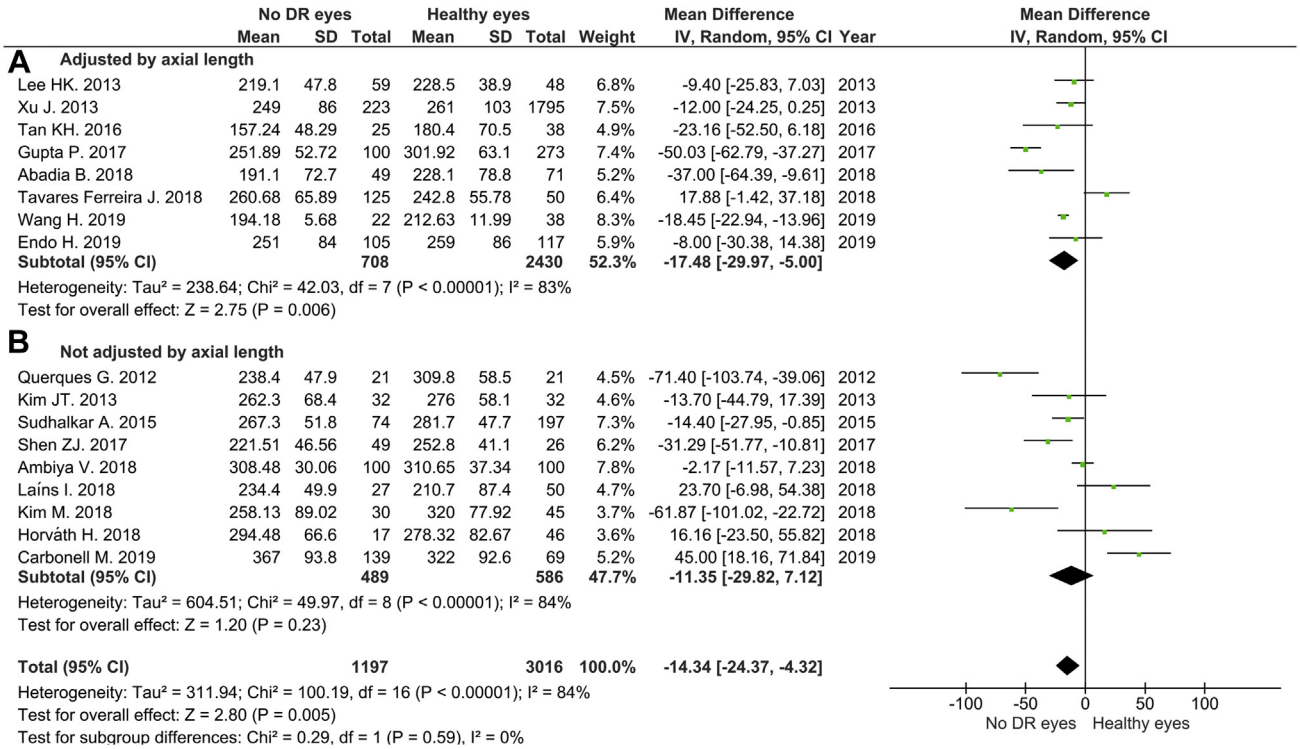


**FIGURE 3. Forest plot to evaluate sub-analysis of subfoveal choroidal thickness (SCT) based on adjustment of axial length. (A) No DR eyes and healthy control eyes with adjusted axial length. (B) No DR eyes and healthy control eyes with unadjusted axial length. The results showed that in the group where axial length was adjusted, SCT of No DR eyes was significantly thinner than that of healthy control eyes. On the other hand, there was no significant difference in the group in which the axial length was not adjusted. CI = confidence interval; DR = diabetic retinopathy; IV = inverse variance; SD = standard deviation.**

*Sub-analysis by HbA1c Levels*. As a significant cause of the heterogeneity between studies, a patient's glycemic control status might be 1 of the potential factors. Of the 8 studies with adjusted axial length, 6 studies described HbA1c values in patients examined. Sub-analyses were performed in 2 groups according to the HbA1c level: HbA1c ≥7% and HbA1c <7%. Of the 6 studies, 5 had HbA1c ≥7% and 1 had HbA1c <7%. Sub-analysis results based on the level of HbA1c value showed that the SCT of NDR was significantly thinner than the healthy control eyes in the HbA1c ≥7% group (WMD = −24.58 μm; 95% CI: −40.37 to −8.79; $P = .002$) (Figure 4A). In contrast, there was no significant difference in the HbA1c <7% group (WMD = −17.88 μm; 95% CI: −1.42 to −37.18; $P = .07$) (Figure 4B).

*Sub-analysis by Duration of Diabetes*. A significant source of heterogeneity between studies may be the duration of diabetes. Of 8 studies with adjusted axial length, 6 studies described the duration of diabetes. Sub-analysis was performed in 2 groups depending on the duration of diabetes: duration of diabetes ≥10 years and <10 years. Sub-analysis based on the duration of diabetes showed that the SCT for the duration of diabetes ≥10 years group was significantly thinner than the healthy control eyes (WMD = −47.71 μm; 95% CI: −59.27 to −36.14; $P < .00001$) (Figure 5A). However, there was no significant difference in the duration of diabetes <10 years group (WMD = −5.99 μm; 95% CI: −21.72 to 9.75; $P = .46$) (Figure 5B).

*Sub-analysis by OCT Instrument Used*. The source of significant heterogeneity between studies may be OCT instrument errors. The study was then stratified based on the OCT instrument used. Of the 8 studies with adjusted axial length, 7 used EDI OCT and 1 used SSOCT. Sub-analyses classified as EDI (WMD = −15.45 μm; 95% CI: −28.73 to −2.17; $P = .02$) (Figure 6A) and SSOCT (WMD = −37.00 μm; 95% CI: −64.39 to −9.61; $P = .008$) (Figure 6B) instruments showed similar results as the main analysis. However, even in this sub-analysis, the significant heterogeneity could not be resolved.

• **PUBLICATION BIAS:** Funnel plots were generated to assess the potential publication bias of the literature (Figure 7). The placement of the data points did not reveal any obvious evidence of asymmetry. In addition, quantitative analyses calculated using Begg's test ($P = .72$) and Egger's test ($P = .73$) showed no clear evidence of publication bias.

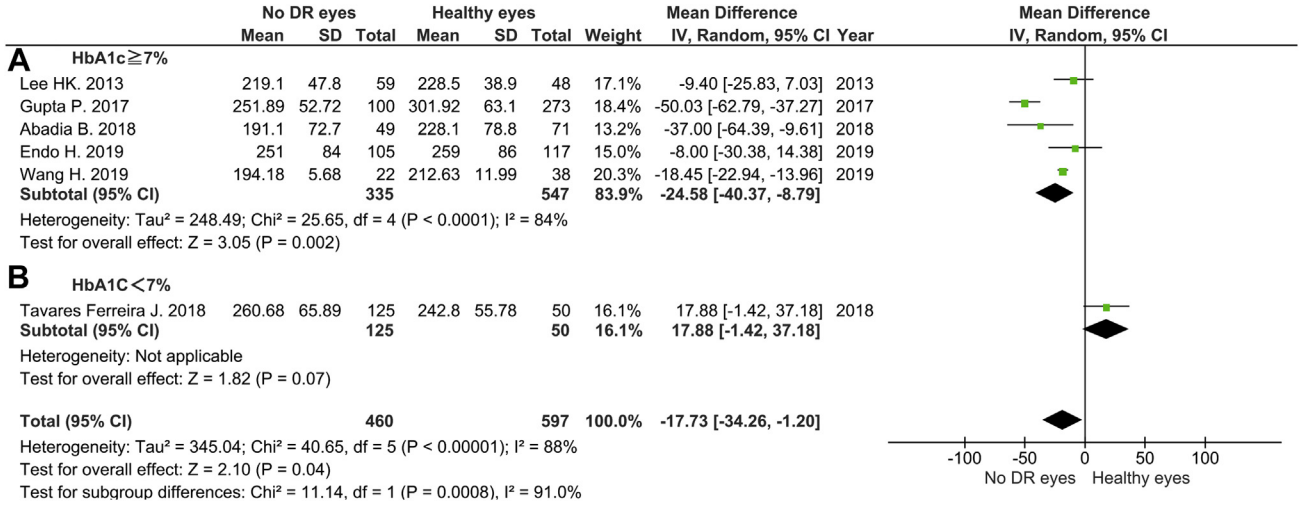


**FIGURE 4. Forest plot evaluates subfoveal choroidal thickness (SCT) sub-analysis based on HbA1c level (limited to studies with adjusted axial length). (A) No DR eyes and healthy control eyes in HbA1c ≥7%. (B) No DR eyes and healthy control eyes in HbA1c < 7%. The results showed that in the HbA1c ≥7% group, SCT of No DR eyes was significantly thinner than SCT of healthy control eyes. On the other hand, there was no significant difference in the HbA1c < 7% group. CI = confidence interval; DR = diabetic retinopathy; IV = inverse variance; SD = standard deviation.**

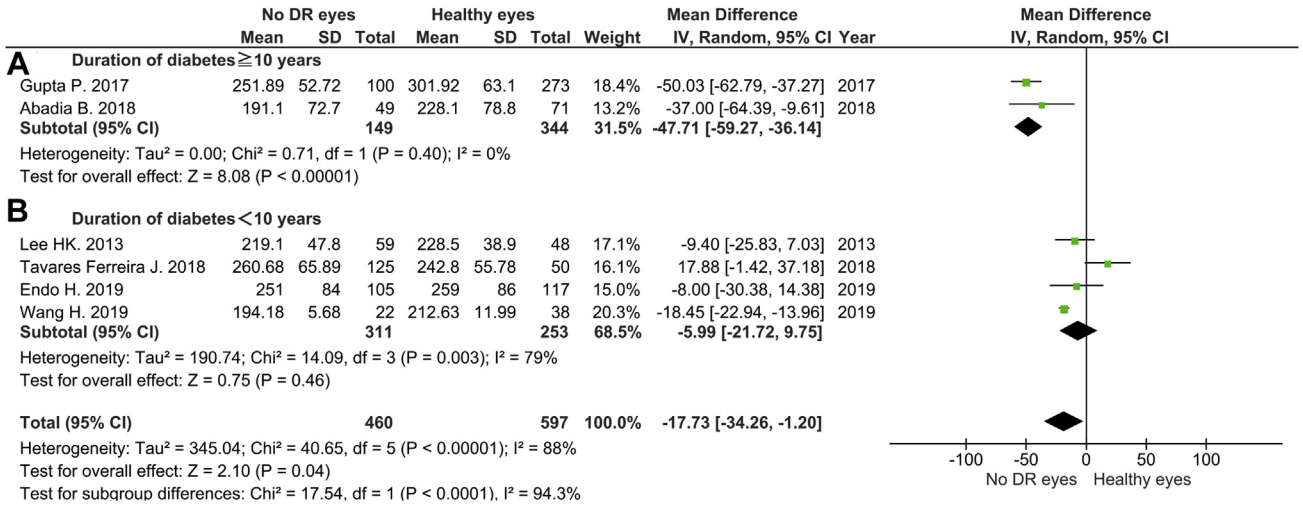


**FIGURE 5. Forest plot evaluates subfoveal choroidal thickness (SCT) sub-analysis based on duration of diabetes (limited to studies with adjusted axial length). (A) No DR eyes and healthy control eyes in duration of diabetes ≥10 years. (B) No DR eyes and healthy control eyes in duration of diabetes < 10 years. The results showed that in the duration of diabetes ≥10 years group, SCT of No DR eyes was significantly thinner than SCT of healthy control eyes. On the other hand, there was no significant difference in the duration of diabetes < 10 years group. CI = confidence interval; DR = diabetic retinopathy; IV = inverse variance; SD = standard deviation.**

## DISCUSSION

THIS META-ANALYSIS REVIEWED 17 RELATED STUDIES, enrolling 4,213 eyes consisting of 1,197 NDR eyes and 3,016 healthy controls eyes. The results of the group comparison were that the SCT of NDR eyes was significantly thinner than healthy control eyes. So far, many of the previous studies were limited by relatively small sample sizes and lacked statistical significance. The meta-analysis in this study could enroll robust number of patients, which eventually provided a more convincing and reliable assessment.

Despite technological advances to investigate retinal structure and function in ocular diseases to date, the true

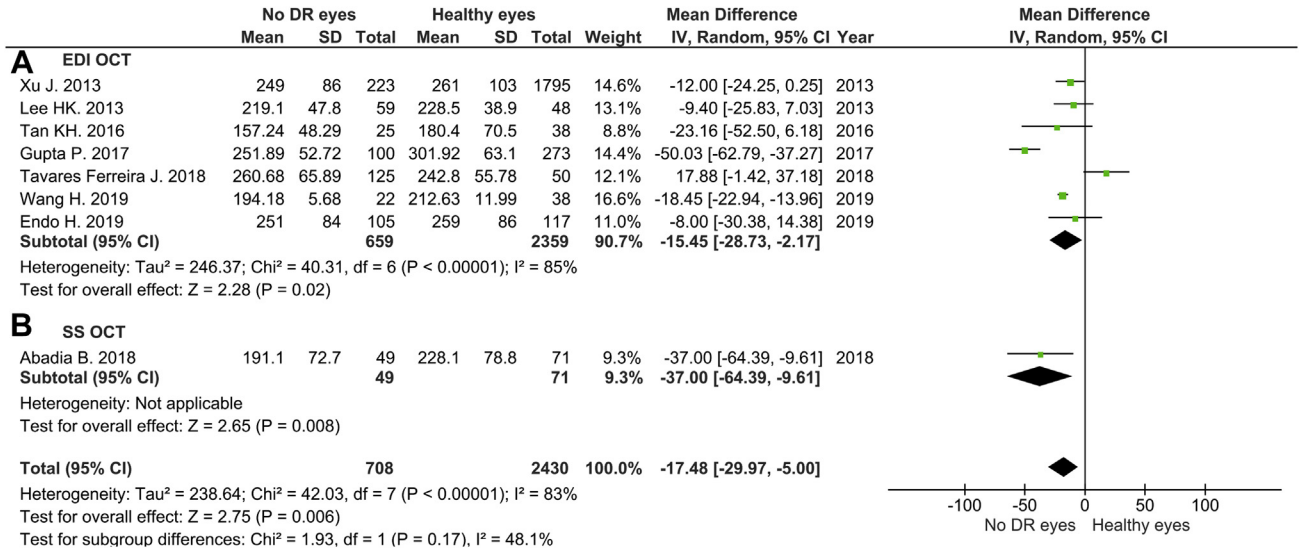


**FIGURE 6. Forest plot evaluate sub-analysis of subfoveal choroidal thickness (SCT) based on optical coherence tomography (OCT) instrument used (limited to studies with adjusted axial length). (A) No DR eyes and healthy control eyes measured by enhanced depth imaging (EDI) OCT. (B) No DR eyes and healthy control eyes measured by swept source (SS) OCT. As a result, in both groups, the SCT of No DR eyes was significantly thinner than the SCT of healthy control eyes. CI = confidence interval; DR = diabetic retinopathy; IV = inverse variance; SD = standard deviation.**

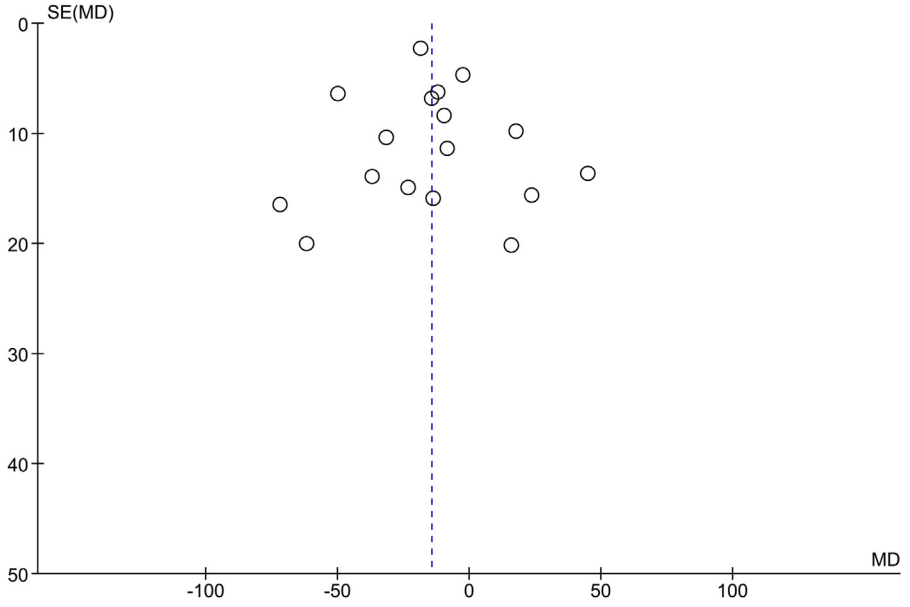


**FIGURE 7. Funnel plot to evaluate publication bias. The data points show symmetry and do not indicate any obvious publication bias.**

pathophysiology of DR is not yet fully understood. Disruption of inner blood-retinal barrier is thought to be an early event in the development of DR[32]; however, several histologic studies have identified vascular changes in the choroid of diabetic eyes.[4–6] The findings in the choroids are similar to those observed in DR: increased vascular tortuosity, microaneurysm formation, areas of nonperfusion, dilations or narrowing of vascular lumens, and choroidal neovascularization. Such pathologic changes primarily affect the choriocapillaris but have been shown to occasionally involve larger choroidal vessels.[33] In addition to the morphologic analyses, choroidal hemodynamics are likely to change even before the onset of DR in DM patients. Studies using laser-

doppler flowmetry stated that increased subfoveal choroidal vascular resistance in diabetic eyes correlated with decreased choroidal blood velocity and blood flow.[7] Moreover, a pulsatile ocular perfusion meter that reflects total choroidal blood flow revealed decrease in total choroidal blood flow of DM eyes without DR.[9] Immunohistochemical studies using postmortem eyes demonstrated increased immunoreactivity for leukocyte adhesion molecules in choroidal blood vessels in DM patients (Background DR or NDR) compared to non-DM patients.[34] As a result, it is likely that these pathophysiological changes in choroidal blood vessels can affect the choroid structure.

With traditional imaging modalities such as indocyanine green angiography and ultrasonography, quantitative assessments of the choroidal structures have been difficult. In recent years, the development of EDI OCT[10] and SSOCT[11] has made it possible to determine SCT quantitatively. In fact, it has also been clarified that the choroidal morphology obtained using OCT technology correlates well with the aforementioned pathologic findings.[35] SCT is the most studied biomarker for choroidal morphologic alterations, which has been measured at the subfoveal levels in most studies. We have reported that SCT varies with the severity of DR.[15,36,37] Thus, OCT techniques are considered to offer excellent reliability, repeatability, and reproducibility for detailed evaluation of the choroid. This meta-analysis proved that the SCT of the NDR eyes was significantly thinner than the healthy control eyes. Therefore, this is the first reliable study to show the choroidal structure changes before the onset of DR.

Measurements of SCT are of importance since variations in SCT might indicate the presence of the disease, predict its progression, or provide insight into its prognosis. For example, it has been reported that SCT decreased in age-related macular degeneration (dry type with geographic atrophy and neovascular type),[38] pathologic myopia,[39] and retinal dystrophy,[40] but increased in central serous chorioretinopathy,[41] polypoidal choroidal vasculopathy,[42] and Vogt-Koyanagi-Harada disease.[43] However, the mechanisms by which SCT fluctuates in DM patients without DR remains unclear. The exact mechanism remains unknown, but the decrease in SCT in NDR eyes might be clinically consistent with pathophysiological findings of choriocapillaris occlusion and/or reduced choroidal circulation in NDR as described before. A manually measured choroidal thickness mapping study with 3D reconstruction of OCT choroidal images reported extensive thinning of the choroid, including the subfoveal region of the NDR.[44,45] Choriocapillaris thickness is about 10 μm, but the thinning seen in the choroidal thickness map exceeds the size of choriocapillaris atrophy, suggesting that it may be related to the loss of choroidal vessels throughout. These results suggest that a decrease in SCT in diabetic eyes may be an indirect biomarker for choroidal circulation disorders. In recent years, an approach has been reported in which the luminal and stromal areas of the choroidal structures are divided using a binarization method in OCT images. In fact, luminal areas observed in OCT measurements could be corresponding to the choroidal vascular components based on histologic observations in cadaver eyes.[35] The ratio of luminal area, referred to as total choroidal area (L/C ratio)[46] or choroidal vascularity index,[47] is calculated as the ratio of luminal area to total choroidal area, and has been proposed as a new index for determining choroidal vascular status. We used this technique to show that although there was no correlation between NDR and SCT, the L/C ratio changed with the duration of diabetes.[16] This probably results from a general decrease in choroidal vessel lumen calibers in diabetic patients. As a future task, it is necessary to verify the correlation between the L/C ratio and histologic sections.

En face imaging is a breakthrough in OCT technology because it allows easy fundus recognition and ideal correlation with multimodal imaging. Ferrara and associates used en face SSOCT to observe choroidal vascular remodeling (irregular tortuous and beaded choroidal vessels with local dilation and narrowing) at all stages of DR including NDR.[48] Murakami and associates examined en face SSOCT images in NDR, demonstrating that the frequency to unvisualized vessels in the Sattler layer, focal vascular narrowing in the Haller layer, and vascular stump in the Haller layer were 17.4%, 48.1%, and 7.4%, respectively.[49] They stated that unvisualized vessels in the Sattler layer observed by the en face SSOCT image may correspond to focal vascular loss or small vessels with obliterated or severely narrowed lumens in the histologic findings of the Sattler layer.[49] Therefore, these choroidal lesions may be associated with changes in SCT.

Recent studies have shown that SCT in healthy eyes varies with age,[50] sex,[51] refraction, axial length,[51] and circadian rhythm.[52] These observations give rise to the possibility that SCT is affected by multiple factors, indicating the importance of the adjustment when researchers compile data on the thickness. In fact, this meta-analysis confirmed 4 studies showing that SCT of NDR eyes was rather thickened, but 3 out of the 4 studies did not adjust axial length. The meta-analysis included age-matched control eyes in all relevant studies, and subgroup analysis was further performed depending on whether the axial length was matched. Another problem was that SCT was associated with HbA1c levels and duration of diabetes. Several studies have shown that SCT is associated with HbA1c levels[21,26,53,54] and duration of diabetes.[20,21] Individual differences in SCT should be avoided by taking into account all confounders as listed. Taken together, this subgroup analysis revealed that there was a significant association between NDR eyes and SCT, when the axial length was correctly adjusted between subjects examined.

The difficulty of meta-analysis is the heterogeneity of existing studies and confounders. Important confounding factors in OCT measurements include coexisting eye conditions such as the stage of DR and axial length, patient

characteristics such as types of DM, HbA1c levels and duration of diabetes, and various OCT instruments. Indeed, adjustments of axial length, HbA1c levels, duration of diabetes, and the OCT-based factors by sub-analysis were correlated with similar results in the main analysis. However, the heterogeneity could nonetheless not be completely resolved. In fact, OCT measurements may lead to meta-analysis heterogeneity depending on patient characteristics such as race, sex, age, and hypertension. Therefore, SCT evaluation will need to be tightly controlled for all variables that may interfere with the results.

Although there are important findings shown here, this meta-analysis has some limitations. First, there was significant heterogeneity in primary analysis studies as discussed above. Factors such as different OCT instruments, different measurement points, and patient characteristics such as race, sex, age, axial length, HbA1c level, and duration of diabetes can lead to meta-analysis heterogeneity. Furthermore, since the choroidal structure is complex and variable, evaluation of the structure might be complemented by the additional imaging data other than local measurements, such as SCT evaluated at a single time point. As a future issue, it is necessary to establish a causal relationship between diabetic subjects and choroidal structure changes based on these data. Second, only published studies are included, and no clear evidence of public bias is presented in the analysis. Therefore, there still may exist potential publication bias. Third, type of DM can affect the SCT, but unfortunately, subgroup analysis regarding DM types was not available owing to lack of the data.

In conclusion, the SCT of NDR eyes was significantly thinner than healthy control eyes. Recent advances in OCT technology have helped to effectively visualize and quantitatively analyze the choroid. The number of studies examining effect of choroidal thickness on DR pathology has increased recently. SCT might be considered an important structural biomarker for the development of DR in diabetic eyes without retinopathy; however, since there was the heterogeneity in primary analysis studies, further confirmations will be necessary.

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## REFERENCES

1. Yau JWY, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35(3):556–564.
2. Antonetti DA, Klein R, Gardner T. Mechanims of disease: diabetic retinopathy. *N Engl J Med* 2012;366(13):1227–1239.
3. Parver LM. Temperature modulating action of choroidal blood flow. *Eye (Lond)* 1991;5(Pt 2):181–185.
4. Hidayat AA, Fine BS. Diabetic choroidopathy. Light and electron microscopic observations of seven cases. *Ophthalmology* 1985;92(4):512–522.
5. Cao J, McLeod S, Merges CA, Lutty GA. Choriocapillaris degeneration and related pathologic changes in human diabetic eyes. *Arch Ophthalmol* 1998;116(5):589–597.
6. Fryczkowski AW, Sato SE, Hodes BL. Changes in the diabetic choroidal vasculature: scanning electron microscopy findings. *Ann Ophthalmol* 1988;20(8):299–305.
7. Nagaoka T, Kitaya N, Sugawara R, et al. Alteration of choroidal circulation in the foveal region in patients with type 2 diabetes. *Br J Ophthalmol* 2004;88(8):1060–1063.
8. Schocket LS, Brucker AJ, Niknam RM, Grunwald JE, DuPont J, Brucker AJ. Foveolar choroidal hemodynamics in proliferative diabetic retinopathy. *Int Ophthalmol* 2004;25(2):89–94.
9. Geyer O, Neudorfer M, Snir T, et al. Pulsatile ocular blood flow in diabetic retinopathy. *Acta Ophthalmol Scand* 1999;77(5):522–525.
10. Spaide RF, Koizumi H, Pozzoni MC, Pozonni MC. Enhanced depth imaging spectral-domain optical coherence tomography. *Am J Ophthalmol* 2008;146(4):496–500.
11. Motaghiannezam R, Schwartz DM, Fraser SE. In vivo human choroidal vascular pattern visualization using high-speed swept-source optical coherence tomography at 1060 nm. *Invest Ophthalmol Vis Sci* 2012;53(4):2337–2348.
12. Querques G, Lattanzio R, Querques L, et al. Enhanced depth imaging optical coherence tomography in type 2 diabetes. *Invest Opthalmol Vis Sci* 2012;53(10):6017.
13. Kim M, Ha MJ, Choi SY, Park Y-H. Choroidal vascularity index in type-2 diabetes analyzed by swept-source optical coherence tomography. *Sci Rep* 2018;8(1):70.
14. Carbonell M, Alonso N, Castelblanco E, et al. Assessment of inner retinal layers and choroidal thickness in type 1 diabetes mellitus: a cross-sectional study. *J Clin Med* 2019;8(9):1412.
15. Kase S, Endo H, Yokoi M, et al. Choroidal thickness in diabetic retinopathy in relation to long-term systemic treatments for diabetes mellitus. *Eur J Ophthalmol* 2016;26(2):158–162.
16. Endo H, Kase S, Ito Y, et al. Relationship between choroidal structure and duration of diabetes. *Graefes Arch Clin Exp Ophthalmol* 2019;257(6):1133–1140.
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25(9):603–605.
18. Lee HK, Lim JW, Shin MC. Comparison of choroidal thickness in patients with diabetes by spectral-domain optical coherence tomography. *Korean J Ophthalmol* 2013;27(6):433.
19. Kim JT, Lee DH, Joe SG, Kim J-G, Yoon YH. Changes in choroidal thickness in relation to the severity of retinopathy and macular edema in type 2 diabetic patients. *Invest Ophthalmol Vis Sci* 2013;54(5):3378–3384.

20. Xu J, Xu L, Du KF, et al. Subfoveal choroidal thickness in diabetes and diabetic retinopathy. *Ophthalmology* 2013;120(10):2023–2028.
21. Sudhalkar A, Chhablani JK, Venkata A, Raman R, Rao PS, Jonnadula GB. Choroidal thickness in diabetic patients of Indian ethnicity. *Indian J Ophthalmol* 2015;63(12):912–916.
22. Tan K-A, Laude A, Yip V, Loo E, Wong EP, Agrawal R. Choroidal vascularity index - a novel optical coherence tomography parameter for disease monitoring in diabetes mellitus? *Acta Ophthalmol* 2016;94(7):e612–e616.
23. Shen Z-J, Yang X-F, Xu J, et al. Association of choroidal thickness with early stages of diabetic retinopathy in type 2 diabetes. *Int J Ophthalmol* 2017;10(4):613–618.
24. Gupta P, Thakku SG, Sabanayagam C, et al. Characterisation of choroidal morphological and vascular features in diabetes and diabetic retinopathy. *Br J Ophthalmol* 2017;101(8):1038–1044.
25. Ambiya V, Kumar A, Baranwal VK, et al. Change in subfoveal choroidal thickness in diabetes and in various grades of diabetic retinopathy. *Int J Retina Vitreous* 2018;4:34.
26. Horváth H, Kovács I, Sándor GL, et al. Choroidal thickness changes in non-treated eyes of patients with diabetes: swept-source optical coherence tomography study. *Acta Diabetol* 2018;55(9):927–934.
27. Abadia B, Suñen I, Calvo P, Bartol F, Verdes G, Ferreras A. Choroidal thickness measured using swept-source optical coherence tomography is reduced in patients with type 2 diabetes. *PLoS One* 2018;13(2):e0191977.
28. Laíns I, Talcott KE, Santos AR, et al. Choroidal thickness in diabetic retinopathy assessed with swept-source optical coherence tomography. *Retina* 2018;38(1):173–182.
29. Tavares Ferreira J, Vicente A, Proença R, et al. Choroidal thickness in diabetic patients without diabetic retinopathy. *Retina* 2018;38(4):795–804.
30. Wang H, Tao Y. Choroidal structural changes correlate with severity of diabetic retinopathy in diabetes mellitus. *BMC Ophthalmol* 2019;19(1):186.
31. Singh SR, Vupparaboina KK, Goud A, Dansingani KK, Chhablani J. Choroidal imaging biomarkers. *Surv Ophthalmol* 2019;64(3):312–333.
32. Cunha-Vaz J, Faria de Abreu JR, Campos AJ. Early breakdown of the blood-retinal barrier in diabetes. *Br J Ophthalmol* 1975;59(11):649–656.
33. Fryczkowski AW, Hodes BL, Walker J. Diabetic choroidal and iris vasculature scanning electron microscopy findings. *Int Ophthalmol* 1989;13(4):269–279.
34. McLeod DS, Lefer DJ, Merges C, Lutty GA. Enhanced expression of intracellular adhesion molecule-1 and P-selectin in the diabetic human retina and choroid. *Am J Pathol* 1995;147(3):642–653.
35. Branchini LA, Adhi M, Regatieri CV, et al. Analysis of choroidal morphologic features and vasculature in healthy eyes using spectral-domain optical coherence tomography. *Ophthalmology* 2013;120(9):1901–1908.
36. Endo H, Kase S, Takahashi M, et al. Alteration of layer thickness in the choroid of diabetic patients. *Clin Exp Ophthalmol* 2018;46(8):926–933.
37. Kase S, Endo H, Takahashi M, et al. Alteration of choroidal vascular structure in diabetic retinopathy. *Br J Ophthalmol* 2020;104(3):417–421.
38. Jirarattanasopa P, Ooto S, Nakata I, et al. Choroidal thickness, vascular hyperpermeability, and complement factor H in age-related macular degeneration and polypoidal choroidal vasculopathy. *Invest Ophthalmol Vis Sci* 2012;53(7):3663–3672.
39. El Matri L, Bouladi M, Chebil A, et al. Choroidal thickness measurement in highly myopic eyes using SD-OCT. *Ophthalmic Surg Lasers Imaging* 2012;43(6 Suppl):S38–S43.
40. Yeoh J, Rahman W, Chen F, et al. Choroidal imaging in inherited retinal disease using the technique of enhanced depth imaging optical coherence tomography. *Graefes Arch Clin Exp Ophthalmol* 2010;248(12):1719–1728.
41. Jirarattanasopa P, Ooto S, Tsujikawa A, et al. Assessment of macular choroidal thickness by optical coherence tomography and angiographic changes in central serous chorioretinopathy. *Ophthalmology* 2012;119(8):1666–1678.
42. Chung SE, Kang SW, Lee JH, Kim YT. Choroidal thickness in polypoidal choroidal vasculopathy and exudative age-related macular degeneration. *Ophthalmology* 2011;118(5):840–845.
43. Maruko I, Iida T, Sugano Y, et al. Subfoveal choroidal thickness after treatment of Vogt-Koyanagi-Harada disease. *Retina* 2011;31(3):510–517.
44. Esmaeelpour M, Považay B, Hermann B, et al. Mapping choroidal and retinal thickness variation in type 2 diabetes using three-dimensional 1060-nm optical coherence tomography. *Invest Ophthalmol Vis Sci* 2011;52(8):5311–5316.
45. Esmaeelpour M, Brunner S, Ansari-Shahrezaei S, et al. Choroidal thinning in diabetes type 1 detected by 3-dimensional 1060 nm optical coherence tomography. *Invest Ophthalmol Vis Sci* 2012;53(11):6803–6809.
46. Sonoda S, Sakamoto T, Yamashita T, et al. Luminal and stromal areas of choroid determined by binarization method of optical coherence tomographic images. *Am J Ophthalmol* 2015;159(6):1123–1131.
47. Agrawal R, Gupta P, Tan KA, Cheung CMG, Wong TY, Cheng CY. Choroidal vascularity index as a measure of vascular status of the choroid: measurements in healthy eyes from a population-based study. *Sci Rep* 2016;6:21090.
48. Ferrara D, Waheed NK, Duker JS, et al. Investigating the choriocapillaris and choroidal vasculature with new optical coherence tomography technologies. *Prog Retin Eye Res* 2016;52:130–155.
49. Murakami T, Uji A, Suzuma K, et al. In vivo choroidal vascular lesions in diabetes on swept-source optical coherence tomography. *PLoS One* 2016;11(8):e0160317.
50. Ooto S, Hangai M, Yoshimura N. Effects of sex and age on the normal retinal and choroidal structures on optical coherence tomography. *Curr Eye Res* 2015;40(2):213–225.
51. Tuncer I, Karahan E, Zengin MO, Atalay E, Polat N. Choroidal thickness in relation to sex, age, refractive error, and axial length in healthy Turkish subjects. *Int Ophthalmol* 2015;35(3):403–410.
52. Tan CS, Ouyang Y, Ruiz H, Sadda SR. Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci* 2012;53(1):261–266.
53. Ünsal E, Eltutar K, Zirtiloğlu S, Dinçer N, Erkul SÖ, Güngel H. Choroidal thickness in patients with diabetic retinopathy. *Clin Ophthalmol* 2014;8:637–642.
54. Torabi H, Isfeedvajani MS, Ramezani M, Daryabari SH. Choroidal thickness and hemoglobin A1c levels in patients with type 2 diabetes mellitus. *J Ophthalmic Vis Res* 2019;14(3):285–290.