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Orginal Article

# Correlation of central corneal thickness with central macular thickness in premature infants

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## Abstract

**Aim:** To evaluate the relationship between the central corneal thickness (CCT) and central macular thickness (CMT) in premature infants.

**Material and Methods:** All infants with a birth weight of less than 2.500 g or with a gestation period of less than 36 weeks were included in the study. Data including birth week, birth weight, age, and body weight at the time of imaging, and weight gain were recorded. The central, superior, nasal, temporal, and inferior macular and corneal thicknesses were measured using the spectral-domain optical coherence tomography (SD-OCT). The correlation between macular and corneal thicknesses and multiple factors including birth week, birth weight, age, and body weight at the time of imaging, and weight gain were analyzed.

**Results:** A total of 74 premature infants were included in the study. The mean birth week and birth weight were 30.5±2.8 weeks and 1520.3±495.3 g, respectively. There were significant positive correlations between the central macular thicknesses and the central (p=0.036, r=0.246), superior (p=0.019, r=0.273), nasal (p=0.035, r=0.248), and inferior (p=0.041, r=0.240) corneal thicknesses. There were significant negative correlations between the central (p=0.021, r=-0.378), superior (p=0.044, r=-0.334), nasal (p=0.002, r=-0.491), inferior (p=0.001, r=-0.526), temporal (p=0.018, r=-0.387) corneal thicknesses and age at the time of imaging.

**Conclusion:** Our study results suggest that there were significant and positive correlations of the central macular thicknesses with the central, superior, nasal and inferior corneal thicknesses. Corneal thickness was significantly negative correlated with age at the time of imaging.

**Keywords:** Cornea; Macula Lutea; Premature Infants.

## INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative retinopathy affecting the retina of premature infants of low birth weight and young gestational age (1). The foveal and macular retinal layers begin to differentiate and become mature 24 to 27 weeks of pregnancy and sustain up to eight months. For the foveal development, centrifugal migration of the inner retina neurons from the foveal center and centripedal migration of the cone cell nucleus toward the foveal center are involved (2,3).

Recent studies have shown that preterm infants have a thicker central macular thickness (CMT) than term infants, irrespective of the presence of ROP, using optical coherence tomography (OCT) (4,5).

In a recent study, premature birth has been associated with the failed migration of the retinal layers from the fovea, which increases the foveal thickness in patients with ROP (6).In another study, the central corneal thickness (CCT) was significantly thicker in premature infants, compared to term infants, indicating that increased birth weight reduces CCT (7). In addition, in premature infants, increased corneal thickness at birth may result in reduced corneal transparency and is possibly related to increased corneal hydration.

The decrease in post-natal hydration is associated with rapid development of endothelium and Na/K ATPase-dependent pump, which leads to a decrease in the corneal thickness (8,9).

The iVue SD-OCT system (Optovue Inc., Fremont, CA, USA) is an optical technique suitable for use in infants that measures CMT and CCT. It is a relatively new system, based on the spectral domain optical coherence (SD-OCT) technology, and was originally developed for posterior segment imaging.

With the introduction of software and connection of the external attachments with lenses, the iVue can obtain

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high-definition cross-sectional images to calculate the thickness of the central and regional cornea.In the present study, we aimed to evaluate the relationship between the CCT and CMT in premature infants.

## MATERIALS and METHODS

The study was approved by the local Ethics Committee and conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. A written informed consent was obtained by the parents or guardians of all participants prior to their inclusion in the study.

A total of randomly selected 74 infants who were under follow-up by the ROP screening program conducted at our institution between December 2016 and April 2017 were included in this study for the measurement of the right eye. Exclusion criteria included anterior segment anomalies, such as congenital glaucoma or Peters' anomaly, and any retinal diseases.

A corneal pachymetry map was created using the Corneal Adapter Module (CAM) version of 3.1.0.17 and the iVue SD-OCT system (Figure 1).

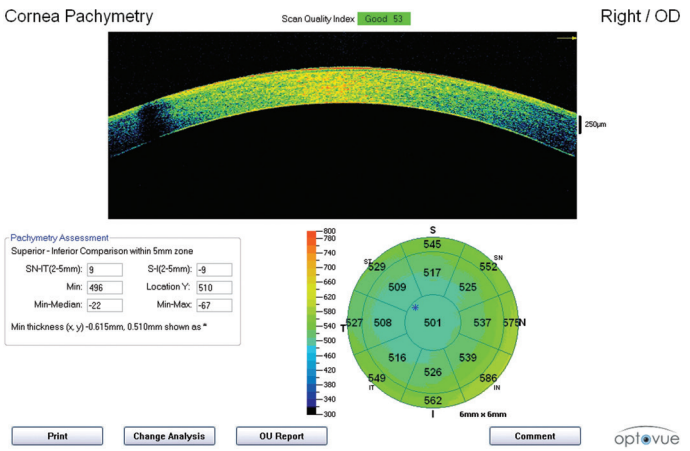


**Figure 1.** Corneal pachymetry map

It operates at 830 nm, a near-infrared wavelength, and can perform 26,000 axial scans of the tissue per second. Before the examination, the iVue system was mounted to the iStand to capture images from the infant in the supine position. One drop of 0.5% proparacaine HCl solution (Alcaine; Alcon Laboratories, Fort Worth, TX, USA) was applied for topical anesthesia.

A pacifier soaked in 30% dextrose was used to calm the baby, when necessary. A lid speculum was used to keep the eyelids open. Three different measurements were obtained from the right eye, when the pupil was in the center of the small diameter circle at the computer monitor connected to the device using the iVue system in the corneal pachymetry mode.

The OCT images were also obtained from the center of fovea by iVue SD-OCT. Retinal map protocol gives us a scan of 2.048 A. Horizontal images 7x6 mm in size at 5 micron resolution were obtained. This gives us a retinal map 1mm and 3mm circle (Figure 2). In all ROP examinations, the central and peripheral fundus was carefully examined through the retinal camera.

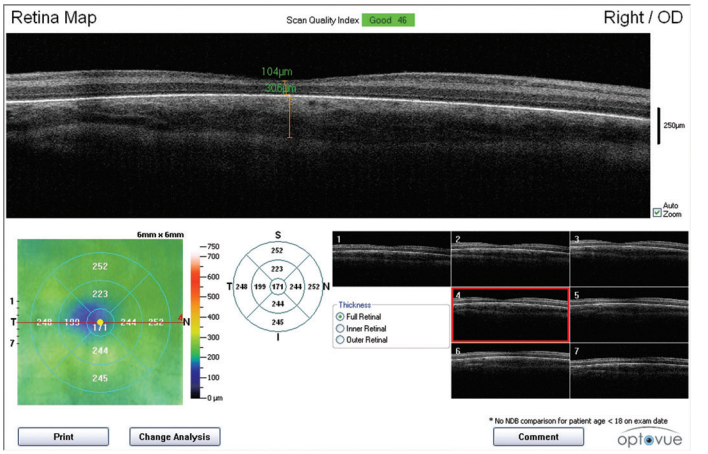


**Figure 2.** Retinal map

Data including birth week, birth weight, age, and body weight at the time of imaging, and weight gain were recorded. Each measurement was obtained at the macula and nasal, temporal, superior, and inferior to the macula. Each measurement was obtained at the cornea and nasal, temporal, superior, and inferior to the cornea. Subfoveal choroidal thickness was also measured as previously described (10). The correlation between the CMT and CCT and multiple factors including the birth week, birth weight, age, and body weight at the time of imaging, and weight gain was also analyzed.

### Statistical Analysis

Statistical analyses were performed using the PS Imago software package (IBM SPSS Statistics Version 23; SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented in terms of the mean ± standard deviation. The correlation between abnormally distributed continuous variables was analyzed using the Spearman's correlation test, while the Pearson's correlation test was used to analyze normally distributed variables. A p value of <0.05 was considered statistically significant.

## RESULTS

A total of 74 premature infants were included in the study. Baseline characteristics of the infants including demographics, birth week, birth weight, age, and body weight at the time of imaging, weight gain and macula and corneal thickness measurements are shown in Table 1.

The mean birth week, birth weight, and age and body weight at the time of imaging were 30.5±2.8 week, 1520.3±495.3 g, 40.4±4.5 week, and 3340.1±920.6 g, respectively. The mean macular thickness at the central, superior, nasal, inferior, and temporal locations was 253.7±90.6 µm 297.0±34.8 µm, 284.8±45.8 µm, 277.4±74.7 µm and 285.4±45.4 µm, respectively. The mean corneal thickness at the central, superior, nasal,

inferior, and temporal locations was 537.2±49.8 µm, 537.9±49.2 µm, 556.0±49.0 µm, 568.8±50.7 µm and 551.9±50.2 µm, respectively.There was a significant positive correlation between the CMT and the central (p=0.036, r=0.246), superior (p=0.019, r=0.273), nasal (p=0.035, r=0.248), and inferior (p=0.041, r=0.240) corneal thicknesses (Table 2).

However, there was no significant correlation between the macular thickness and the birth week, age and body weight at the time of imaging, and weight gain (Table 3).

There was also a significant negative correlation between the central (p=0.021, r=-0.378), superior (p=0.044, r=-0.334), nasal (p=0.002, r=-0.491), inferior (p=0.001, r=-0.526), and temporal (p=0.018, r=-0.387) corneal thickness and the age at the time of imaging.

We also found a significant negative correlation between the nasal (p=0.012, r=-0.420), inferior (p=0.017, r=-0.401) and temporal (p=0.041, r=-0.347) corneal thickness and the weight gain (Table 4).

However, there was no significant correlation between the subfoveal choroidal thickness and the CMT (p=0.398, r=-0.103) and CCT (p=0.803, r=0.030).

**Table 1. Demographic and clinical characteristics of premature infants**

| | Premature infants(n=74 ) |
|---|---|
| | Mean±SD |
| Birth week (week) | 30.5±2.8 |
| Birth weight (g) | 1520.3±495.3 |
| Age at the time of imaging (week) | 40.4±4.5 |
| Body weight at the time of imaging (g) | 3340.1±920.6 |
| Macular thickness (µm) | |
| Central | 253.7±90.6 |
| Superior | 297.0±34.8 |
| Nasal | 284.8±45.8 |
| Inferior | 277.4±74.7 |
| Temporal | 285.4±45.4 |
| Corneal thickness (µm) | |
| Central | 537.2±49.8 |
| Superior | 537.9±49.2 |
| Nasal | 556.0±49.0 |
| Inferior | 568.8±50.7 |
| Temporal | 551.9±50.2 |
| Subfoveal choroid thickness (µm) | 348.3±78.7 |

**Table 2. Correlation between corneal thickness and macula thickness according to location**

| | Corneal thickness | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Central | | Superior | | Nasal | | Inferior | | Temporal | |
| | p | r | p | r | p | r | p | r | p | r |
| Macular thickness | | | | | | | | | | |
| Central* | 0.036 | 0.246 | 0.019 | 0.273 | 0.035 | 0.248 | 0.041 | 0.240 | 0.056 | 0.225 |
| Superior# | 0.887 | -0.017 | 0.730 | 0.041 | 0.623 | -0.058 | 0.590 | -0.064 | 0.850 | 0.023 |
| Nasal* | 0.801 | 0.030 | 0.898 | 0.015 | 0.782 | -0.033 | 0.499 | 0.080 | 0.437 | 0.092 |
| Inferior# | 0.358 | 0.109 | 0.262 | 0.133 | 0.380 | 0.104 | 0.315 | 0.119 | 0.354 | 0.110 |
| Temporal* | 0.392 | 0.102 | 0.536 | 0.074 | 0.584 | 0.065 | 0.252 | 0.136 | 0.189 | 0.156 |

*Results obtained by Spearman correlation test,
#Results obtained by Pearson correlation test.

**Table 3. Correlation between macular thicknesses and birth week, birth weight, age and body weight at the time of imaging, and weight gain**

| | Macular thickness | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Central | | Superior | | Nasal | | Inferior | | Temporal | |
| | p | r | p | r | p | r | p | r | p | r |
| Birth week | 0.901 | -0.021 | 0.287 | 0.180 | 0.582 | 0.093 | 0.681 | 0.070 | 0.125 | 0.257 |
| Birth weight | 0.830 | -0.037 | 0.205 | 0.213 | 0.849 | 0.032 | 0.361 | 0.155 | 0.026 | 0.366 |
| Age at the time of imaging | 0.882 | -0.025 | 0.768 | 0.050 | 0.806 | -0.042 | 0.893 | -0.023 | 0.116 | -0.263 |
| Body weight at the time of imaging | 0.795 | -0.045 | 0.568 | 0.098 | 0.650 | -0.078 | 0.989 | -0.002 | 0.228 | -0.206 |
| Weight gain | 0.899 | -0.022 | 0.925 | 0.016 | 0.682 | -0.071 | 0.765 | -0.052 | 0.061 | -0.315 |

Results obtained by Pearson correlation test.

**Table 4. Correlation between corneal thicknesses and birth week, birth weight, age and body weight at the time of imaging, and weight gain**

| | Corneal thickness | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Central | | Superior | | Nasal | | Inferior | | Temporal | |
| | p | r | p | r | p | r | p | r | p | r |
| Birth week | 0.846 | 0.033 | 0.682 | -0.070 | 0.995 | -0.001 | 0.990 | 0.002 | 0.746 | 0.055 |
| Birth weight | 0.260 | 0.190 | 0.774 | 0.049 | 0.445 | 0.129 | 0.457 | 0.126 | 0.214 | 0.209 |
| Age at the time of imaging | 0.021 | -0.378 | 0.044 | -0.334 | 0.002 | -0.491 | 0.001 | -0.526 | 0.018 | -0.387 |
| Body weight at the time of imaging | 0.179 | -0.232 | 0.245 | -0.202 | 0.028 | -0.372 | 0.035 | -0.357 | 0.094 | -0.288 |
| Weight gain | 0.071 | -0.309 | 0.130 | -0.261 | 0.012 | -0.420 | 0.017 | -0.401 | 0.041 | -0.347 |

Results obtained by Pearson correlation test

## DISCUSSION

To the best of our knowledge, this is the first study to evaluate the relationship between the CCT and CMT in premature infants.

Retinopathy of prematurity is a disease affecting the anterior and posterior segments of the eye. Premature infants less than 30 weeks have a cloudy cornea, which precludes fundus examination in the majority of infants. Central corneal hydration plays an important role in determining the corneal thickness of premature infants. A cloudy cornea is typical in premature infants with decreased corneal transparency. However, corneal transparency develops during the fetal life. Due to some ultra-structural mechanisms, such as the stromal matrix compaction and bioassembly, the transparent cornea becomes permanent after the regulation of uniform and fine collagen fibrils (8).

In a study, Kirwan et al. (11) reported that premature infants at 31 weeks of gestation had a thick cornea, and the corneal thickness decreased dramatically between this period and term period. An increase in the corneal diameter and a decrease in the corneal curvature by providing remodeling and stretching of the collagen fibers may result in a decrease in the corneal thickness, which plays a major role in the corneal development after birth.

Fovea is immature at birth (2,3). Histological findings reported by Mann in 1964 (12) were as follows:1) the persistence of the inner retinal layers in the foveal center and the absence of normal foveal curvature in the fetal eye; and 2) changes in the width and the length of the photoreceptor substructures over time. Foveal maturation process has been described as centrifugal migration of the inner retinal layers and centripedal migration of cone cells (8-10). The number of foveal cone nuclei increases from a single layer to four to eight layers at about 22th week in the completely mature macula, although the cones slowly become thinner and elongate for at least 45 months after birth (3). After birth, it is considered that the foveal pit continues to become remodeled and reaches maturity by 18 months of age (13).

Previous studies have revealed that the shallow foveal pit is associated with the gestational age at birth in preterm infants (4,6). This can be explained by the inability of the inner retinal layers to migrate away from the fovea in preterm infants. Wang et al. (6) reported that the differences in the retinal thickness between preterm and term infants were affected by the inner retinal layers, rather than the outer layers. The fovea of premature infants is significantly thicker than the term infants (5).

Early OCT studies in preterm infants and adults with regressed ROP demonstrated blunted or absent foveal depressions and presence of persisting inner retinal layers, including the inner plexiform and the inner nuclear layers ("inner retinal immaturity") and increased retinal thickness at the fovea (4,14-16). The variability in the formation of foveal remodeling during development may lead to macular edema and increased macular thickness in premature infants. However, Moldonado et al. (17) suggested that this might be associated with higher vascular endothelial growth factor (VEGF) levels in the eye, similar to adult cystoid macular edema, which response to anti-VEGF therapy. In the histological studies of foveal development, there was an increased expression of VEGF messenger ribonucleic acid (mRNA) in the early developing fovea, despite the absence of macular edema (18), and increased intraocular VEGF levels were detected in the eyes operated for advanced ROP (19).

In humans, in the retinal and choroidal vascular endothelium, and in the retinal pigment epithelium, VEGF expression has been detected. VEGF and its receptors are located in the corneal epithelium, stroma, and endothelium; therefore, cornea can be affected by anti-VEGF treatments (20,21). In a study, Philipp et al. (22) showed that VEGF was expressed in the epithelial and endothelial cells of cornea, vascular endothelial cells of limbal vessels, and keratinocytes in normal human corneas of donor eyes. Vinekar et al. (23) also suggested that macular edema might be associated with VEGF in prematurity. We also consider that corneal edema in prematurity may be associated with VEGF. Increased VEGF levels may be responsible for both macular thickness and corneal thickness in premature infants.

Considering the finding that the density of the retinal pigment epithelium cells was low in premature infants (24), Erol et al. (25) reported that low RPE cell density might

contribute to the formation of cystoid macular edema in premature infants, increasing the macular thickness. The decrease in corneal transparency after birth may be associated with slow development of the endothelium and Na/KATPase-dependent pump in the premature baby, leading to an increase in the corneal thickness.

Furthermore, there are significant similarities between the corneal endothelium and retinal pigment epithelium cells in terms of embryology, barrier function, and susceptibility to age-related degenerative changes. Both are located on the basement membranes, that is, Descemet's and Bruch's; both have tight junctions between their cells, and both have active cell transport systems involving Na-KATPase and anionic pumps. In addition, both the corneal endothelium and retinal pigment epithelium cells are prone to age-related degeneration (26).

In our study, there was a significant positive correlation between the CMT and the central, superior, nasal, and inferior corneal thicknesses. In addition, corneal thickness was significantly and negatively correlated with the age at the time of imaging.

In this study, there were several limitations, including a short study period, and it is a single-center study and has a relatively small sample size.

In conclusion, our study results suggest that, in premature infants, the variability in the formation of foveal and corneal remodeling during development may lead to increased macular thickness and corneal thickness. Increased VEGF levels may be responsible for both macular thickness and corneal thickness in premature infants. There are significant similarities between the corneal endothelium and retinal pigment epithelium cells. Macular thickness and corneal thickness may be affected by similar mechanisms.

*Competing interests: The authors declare that they have no competing interest.*

*Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.*

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