Ultrasonographic measurement of the optic nerve sheath diameter and its association with eyeball transverse diameter in 585 healthy volunteers

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The optic nerve sheath diameter (ONSD) is considered as an indirect marker for intracranial pressure (ICP). However, the optimal cut-off value for an abnormal ONSD indicating elevated ICP and its associated factors have been unclear. Thus, we investigated normative values for the ONSD using ultrasonography and investigate the potential factors affecting it. We prospectively recruited healthy volunteers between September 2016 and March 2017. A total of 585 individuals were included, in which the mean ONSD was 4.11 mm (95% confidence interval (CI), 4.09–4.14 mm). Although ONSD was correlated with sex (p = 0.015), height (p = 0.003), and eyeball transverse diameter (ETD) (p < 0.001) in simple linear regression analyses, multiple linear regression analysis revealed that only ETD was independently associated with ONSD (p < 0.001). Accordingly, we further established a normative value for the ONSD/ETD ratio and its associated factors. The mean ONSD/ETD ratio was 0.18 (95% CI, 0.18–0.18), but the ONSD/ETD ratio was not correlated with sex, height, weight, body mass index, and head circumference. Our findings suggest that the ONSD had a strong correlation with ETD, and ONSD/ETD ratio might provide more reliable data than ONSD itself as a marker of ICP.

Elevated intracranial pressure (ICP) is a potentially devastating condition resulting from various neurological and non-neurological disorders1. Rapid detection of elevated ICP and subsequent management are important because it is associated with poor prognosis2,3. The golden standard for estimating ICP includes invasive methods such as intraventricular catheterization and intraparenchymal probes4. However, such procedures are not routinely performed because of the absence of neurosurgeons or intensive care units and the risk of complications including hemorrhage and infection. In addition, they are contraindicated in patients with thrombocytopenia or coagulopathy5,6. Accordingly, the importance of non-invasive methods for ICP measurement has increased.

The optic nerve sheath diameter (ONSD) is considered as an indirect marker for ICP estimation7. Measurement of ONSD by ultrasonography is a rapid and easily accessible bedside test. Furthermore, growing evidence has shown that this procedure has high reproducibility and low intra- and inter-observer variability8,9. Given that computed tomography (CT) or magnetic resonance imaging is time consuming and requires patient transfer, ultrasonographic measurement of ONSD may be a good choice for the detection of elevated ICP in clinical settings and research. However, despite its usefulness and popularity, the optimal cut-off value for an abnormal ONSD indicating elevated ICP has been unclear, because most studies on ONSD measurement included only a small number of healthy individuals. Furthermore, although previous studies investigated demographic and physiological factors associated with ONSD, the results have been inconsistent or inconclusive. A clear understanding of the normal range for ONSD and its associated factors is crucial to interpret the measurement as a marker of ICP.

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Therefore, the main aims of the current study were to establish normative values for ONSD using ultrasonography in a large number of healthy Korean adults and investigate potential factors affecting this parameter.

**Materials and Methods**

**Study Population.** We prospectively recruited healthy volunteers who visited the Republic of Korea Air Force Education And Training Command for physical examination required to become a soldier between September 2016 and March 2017. All volunteers were limited to young healthy adults aged 18–30 years, given the nature of the military organization. We excluded individuals with a history of neurological disorders. Written informed consent was obtained from all participants before enrollment. The study protocol was approved by the Institutional Review Board of the Armed Forces Medical Command (Seongnam, Korea) and followed to the principles of the Declaration of Helsinki.

The following data were recorded for each subject: age, sex, height, weight, and head circumference. The head circumference was measured by a single investigator (R.K., a board-certified neurologist) using a nonstretchable tape around the widest possible occipitofrontal circumference. The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared.

**Ultrasound Measurement.** Ultrasonic examination was performed by an experienced investigator (D.H.K., a board-certified radiologist) using a GE Logiq P6 scanner (General Electrics Medical Systems, Milwaukee, WI, USA) with a 11–3 MHz linear transducer. The subjects were examined in a supine position with the head elevated at 20–30°. They were instructed to keep their eyes shut in a mid-position of the bulb and suppress any eye movement. A thick layer of conductive ultrasound gel was applied over the closed upper eyelid. The probe was placed gently on the gel in the temporal area of the eyelid to prevent pressure from being exerted on the eye.

ONSD and the eyeball transverse diameter (ETD) were measured for each eye in the horizontal plane (Fig. 1). ONSD was defined as the distance between the external borders of the hyperechoic area 3 mm posterior to the point where the optic nerve entered the globe, using an electronic caliper along the axis perpendicular to the retina. ETD (retina to retina) was defined as the maximal transverse diameter of the eyeball obtained by scanning from the superior to the inferior side. To minimize intraobserver variability, each measurement was performed three times and the mean value was derived. Before the enrollment of participants, a training session with 15 healthy volunteers who were not included in this study was held to familiarize the examiner with the ultrasonic measurement of ONSD and ETD.

**Statistical Analysis.** Continuous variables are presented as medians and interquartile ranges (IQRs) or means ± standard deviations (SDs), while categorical variables are reported as frequencies and percentages. Continuous variables were compared using paired t-tests. We used a series of simple linear regression models to identify demographic and physiological factors associated with ONSD. Potential factors of interest were selected a priori on the basis of previous literature; these included sex, height, weight, BMI, head circumference, and ETD. The factors that survived simple linear regression analyses were then evaluated using multiple linear regression models. A two-tailed p-value of <0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS version 18 (IBM Software Inc.).

**Results**

In total, 585 healthy volunteers were included in this study. The mean age was 21.4 ± 1.9 years, and 508 (90.4%) subjects were men. The mean height, weight, BMI, and head circumference of the individuals were 171.1 ± 6.8 cm, 68.5 ± 11.6 kg, 22.8 ± 3.1 kg/m², and 57.6 ± 1.7 cm, respectively.

ONSD and ETD values are detailed in Table 1. ONSD ranged from 3.30 mm to 5.20 mm, and 95% subjects exhibited a mean ONSD in the range of 4.09 mm to 4.14 mm. The median ONSD was 4.10 mm (IQR,
There was no significant difference in ONSD between the right and left eyes ($p = 0.510$). The median and mean ETD were 22.85 mm (IQR, 22.25–23.45 mm) and 22.91 ± 0.93 mm, respectively.

The results of regression analyses are summarized in Table 2. Simple linear regression analyses showed that ONSD was correlated with sex ($p = 0.015$), height ($p = 0.003$), and ETD ($p < 0.001$). After adjustment for potential confounders between these factors, only ETD was found to be independently associated with ONSD ($p < 0.001$). Accordingly, we further analyzed normative values for the ONSD/ETD ratio and its associated factors including sex, height, weight, BMI, and head circumference. The ONSD/ETD ratio ranged from 0.14 to 0.23, and 95% subjects exhibited a mean ONSD/ETD ratio of 0.18. There was no significant difference in the ONSD/ETD ratio between the right and left eyes ($p = 0.329$). Simple linear regression analyses showed that the ONSD/ETD ratio was not correlated with sex ($p = 0.140$), height ($p = 0.505$), weight ($p = 0.826$), BMI ($p = 0.516$), and head circumference ($p = 0.387$).

Discussion
In the present study, we assessed normative values for ONSD and its associated factors using ultrasonography in 585 healthy Korean adults. The mean [95% confidence interval (CI)] values for ONSD, ETD, and the ONSD/ETD ratio were 4.11 ± 0.35 mm (4.09–4.14 mm), 22.91 ± 0.93 mm (22.83–22.98 mm), and 0.18 ± 0.02 (0.18–0.19), respectively, and ONSD was associated with ETD, but not with sex, height, weight, BMI, and head circumference. To our knowledge, the present study included the largest number of healthy volunteers among all studies evaluating ONSD using ultrasonography. Therefore, we believe that our findings regarding the normal range for ONSD and its associated factors are reliable.

The mean ultrasonographic ONSD in the current study was 4.11 mm (range, 3.3–5.2 mm); this value is close to that reported by Lee et al., who reported a mean CT-based ONSD of 4.1 mm (range, 2.9–5.3 mm) in the Korean population. The normal range for ultrasonographic ONSD in healthy volunteers has been reported in many other countries (Table 3). Despite the diversity in the results of these studies, the ONSD measurements in this study were within the normal range of previously reported values. In addition, the upper normal ONSD limit (5.2 mm) and the upper bound of the 95% CI (4.14 mm) for the mean ONSD value corroborated with the optimal cut-off value for the identification of elevated ICP suggested by previous studies where the lowest bound of ONSD values was ≥5.2 mm in patients with elevated ICP. Although some authors insist that ONSD is influenced by ethnicity, we could not find obvious differences between Korea and other countries.

### Table 1. Basic descriptive statistics for ONSD, ETD, and the ONSD/ETD ratio measured using ultrasonography for healthy Korean adults. The overall ONSD value is the mean of the values for the left and right eyes. ONSD, optic nerve sheath diameter; ETD, eyeball transverse diameter; SD, standard deviation; CI, confidence interval; IQR, interquartile range.

| Variables | Simple linear regression analysis | Multiple linear regression analysis |
|-----------|----------------------------------|-----------------------------------|
|           | B-Coefficient | SE | $P$   | B-Coefficient | SE | $P$ |
| Sex       | −0.121        | 0.050 | 0.015 | −0.069        | 0.057 | 0.224 |
| Height    | 0.006         | 0.002 | 0.003 | 0.003         | 0.002 | 0.310 |
| Weight    | 0.002         | 0.001 | 0.098 | —             | — | — |
| BMI       | 0.002         | 0.005 | 0.683 | —             | — | — |
| HC        | 0.012         | 0.008 | 0.171 | —             | — | — |
| ETD       | 0.088         | 0.015 | <0.001 | 0.083         | 0.016 | <0.001 |

### Table 2. Finding of linear regression analyses for potential factors associated with ONSD. ONSD, optic nerve sheath diameter; BMI, body mass index; HC, head circumference; ETD, eyeball transverse diameter; SE, standard error.
### Table 3. Summary of published studies estimating ONSD using ultrasonography in healthy volunteers. *Data are number of healthy volunteers. ONSD, optic nerve sheath diameter; SD, standard deviation; CI, confidence interval; NA, not applicable; HC, head circumference; ONSD, optic nerve diameter; ETD, eyeball transverse diameter; BMI, body mass index; MABP, mean arterial blood pressure; IQR, interquartile range.

| Author (Reference) | Nation | Number (years) | Mean ± SD (95% CI) | Range | Associated factor | Non-associated factor |
|--------------------|--------|----------------|--------------------|-------|------------------|----------------------|
| **Asian population** | | | | | | |
| Maade14 Bangladesh 136 (NA) | 4.41 (4.25–4.75) mm | 4.24–4.83 mm | NA | Sex, age, HC | |
| Shirodkar15 India 41 (27.4) | F: 4.63 ± 0.09 (4.59–4.67) mm M: 4.80 ± 0.10 (4.76–4.84) mm | NA | NA | NA | |
| Chen15 China 519 (46.1) | 5.1 ± 0.5 (5.06–5.14) mm | 3.5–6.4 mm | ONSD | Sex, age, weight, height, ETD | |
| Wang14 China 230 (43.2) | 3.46 ± 0.28 (3.42–3.49) mm | 2.65–4.30 mm | Sex, BMI | Age, HC, waistline, MABP | |
| Amini16 Iran 32 (59.5) | 3.2 ± 0.3 (3.1–3.3) mm | 2.6–4.1 mm | NA | NA | |
| Rehman16 Pakistan 26 (34.7) | 4.33 ± 0.38 (4.18–4.48) mm | NA | NA | NA | |
| Current study South Korea 585 (21.4) | 4.11 ± 0.35 (4.09–4.14) mm | 3.30–5.20 mm | ETD | Sex, weight, height, BMI, HC | |
| **Western population** | | | | | | |
| Ballantyne17 UK 67 (37) | 3.2–3.6 mm | 2.4–4.7 mm | NA | NA | |
| Romagnuolo18 USA 10 (NA) | Lt.: 4.6 ± 0.71 (4.09–5.11) mmLt.; 4.5 ± 0.56 (4.1–4.9) mm | NA | NA | Position | |
| Blehar18 USA 27 (36.6) | 4.3 (4.0–4.7) mm | NA | NA | NA | |
| Shah19 USA 40 | 3.7±3.92 mm | NA | NA | NA | |
| Skoloudik20 Czech Republic 16 (68.6) | 3.41 mm | NA | NA | NA | |
| Bauerle9 Germany 40 (37.1) | 5.4 ± 0.6 (5.2–5.6) mm | 4.3–7.6 mm | NA | Sex, BMI | |
| Bauerle21 Germany 15 (24.5) | 5.43 ± 0.49 (5.18–5.68) mm | 4.6–6.4 mm | NA | NA | |
| Strapazzon21 Italy 19 (39.5) | 5.45 ± 0.29 (5.32–5.58) mm | 4.85–5.94 mm | Hypobaric hypoxia | NA | |
| Lochner22 Italy 21 (34.2) | Median: 5.2 (IQR: 4.8–5.5) mm | NA | Sex | age | |
| Lochner22 Italy 20 (46.3) | 5.95 ± 0.68 (5.65–6.25) mm | 4.5–7.7 mm | NA | NA | |
| Amini15 USA 42 (24) | Rt.: 4.73 ± 0.73 (4.50–4.96) mmLt.: 4.48 ± 0.62 (4.28–4.68) mm | NA | NA | NA | |
| Leffert26 USA 20 (24) | 4.99 ± 0.68 (4.69–5.29) mm | NA | NA | Acute resistance exercise | |
| Goeres27 Canada 120 (29.3) | 3.68 ± 0.36 (2.85–4.40) mm | NA | Sex | Age, weight, height | |
| Zeiler28 Canada 120 (29.3) | 3.68 (2.85–4.40) mm | NA | NA | NA | |
| Dinsmore29 Canada 11 (33.5) | 4.2 ± 0.7 (3.8–4.6) mm | NA | End-tidal PCO₂ | NA | |

There was a strong correlation between ONSD and ETD in the present study, and this finding is supported by a previous study evaluating CT-based ONSD.14 Several studies have assessed the relationship between sex and ONSD, although the results have been inconsistent (Table 3).38,11,13,14,24,27. We found an association between sex and ONSD in our simple regression analyses but not in our multiple regression analyses including ETD. This finding strongly suggests that sex is not associated with ONSD, and ETD is a confounding factor for their relationship. Weight was not associated with ONSD in the current study, which is consistent with the results of previous studies.39,40 The ultrasonographic ONSD/ETD ratio may be a better marker of elevated ICP compared with ONSD alone for several reasons. First, there was a strong correlation between ONSD and ETD. Second, the standard deviation between the normative and pathological values for ONSD was overlapping. Finally, the ONSD/ETD ratio was independent of demographic factors such as sex, height, weight, and BMI. Further trials are warranted to validate this parameter in patients with elevated ICP.41–45,22. The derived ratio is very similar to the CT-based ratio of 0.19 derived by Vaiman et al.37, who also found that the ONSD/ETD ratio was significantly higher in patients with intracerebral hemorrhage than in healthy individuals and exhibited a reasonably good correlation with invasive ICP values.38,40. The ultrasonographic ONSD/ETD ratio may be a better marker of elevated ICP compared with ONSD alone for several reasons. First, there was a strong correlation between ONSD and ETD. Second, the standard deviation between the normative and pathological values for ONSD was overlapping. Finally, the ONSD/ETD ratio was independent of demographic factors such as sex, height, weight, and BMI. Further trials are warranted to validate this parameter in patients with elevated ICP.22.
results of the straight and lateral gaze tests with B-mode ultrasound in healthy subjects. Thus, we measured the ONSD in the straight gaze position.

This study has some limitations. Ultrasonographic measurements were obtained by a single experienced board-certified radiologist; therefore, interobserver variability was not evaluated in this study. However, each measurement was obtained three times to minimize errors and bias. In addition, all volunteers were limited to young healthy adults; therefore, the generalizability of our findings to populations of all ages is limited. However, many previous studies have reported that ONSD is not associated with age, and some authors have suggested that ONSD remains more or less constant during the life of an individual. Accordingly, this limitation is not likely to be significant.

In conclusion, we found that the mean ONSD and the ONSD/ETD ratio determined using ultrasonography in healthy Korean adults were 4.11 mm (95% CI, 4.09–4.14 mm; IQR, 3.85–4.35 mm) and 0.18 (95% CI, 0.18–0.18; IQR, 0.17–0.19), respectively. ONSD exhibited a strong correlation with ETD, but not with sex, height, weight, BMI, and head circumference. Our findings suggest that the ONSD/ETD ratio measured using ultrasonography may be a more accurate and helpful marker of elevated ICP compared with ONSD alone, which is further investigated in the future study.

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Author Contributions
Dr. D.H. Kim designed the research, acquired and analyzed the data and drafted the manuscript. Dr. J.S. Jun made critical revisions to the manuscript. Dr. R. Kim designed the research, analyzed the data, and made critical revisions to the manuscript.

Additional Information
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