Brief Research Report | Breast Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2023.1189
Korean J Radiol 2024;25(6):511-517

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Korean Journal of Radiology
KJR

Background Breast Parenchymal Signal During Menstrual Cycle on Diffusion-Weighted MRI: A Prospective Study in Healthy Premenopausal Women

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Objective: To prospectively investigate the influence of the menstrual cycle on the background parenchymal signal (BPS) and apparent diffusion coefficient (ADC) of the breast on diffusion-weighted MRI (DW-MRI) in healthy premenopausal women.
Materials and Methods: Seven healthy premenopausal women (median age, 37 years; range, 33–49 years) with regular menstrual cycles participated in this study. DW-MRI was performed during each of the four phases of the menstrual cycle (four examinations in total). Three radiologists independently assessed the BPS visual grade on images with b-values of 800 sec/mm^2 (b800), 1200 sec/mm^2 (b1200), and a synthetic 1500 sec/mm^2 (sb1500). Additionally, one radiologist conducted a quantitative analysis to measure the BPS volume (%) and ADC values of the BPS (ADC_{BPS}) and fibroglandular tissue (ADC_{FGT}). Changes in the visual grade, BPS volume (%), ADC_{BPS}, and ADC_{FGT} during the menstrual cycle were descriptively analyzed.
Results: The visual grade of BPS in seven women varied from mild to marked on b800 and from minimal to moderate on b1200 and sb1500. As the b-value increased, the visual grade of BPS decreased. On b800 and sb1500, two of the seven volunteers showed the highest visual grade in the early follicular phase (EFP). On b1200, three of the seven volunteers showed the highest visual grades in EFP. The BPS volume (%) on b800 and b1200 showed the highest value in three of the six volunteers with dense breasts in EFP. Three of the seven volunteers showed the lowest ADC_{BPS} in the EFP. Four of the seven volunteers showed the highest ADC_{BPS} in the early luteal phase (ELP) and the lowest ADC_{FGT} in the late follicular phase (LFP).
Conclusion: Most volunteers did not exhibit specific BPS patterns during their menstrual cycles. However, the highest BPS and lowest ADC_{BPS} were more frequently observed in EFP than in the other menstrual cycle phases, whereas the highest ADC_{BPS} was more common in ELP. The lowest ADC_{FGT} was more frequent in LFP.
Keywords: Apparent diffusion coefficient; Background parenchymal signal; Breast cancer; Menstrual cycle; Diffusion magnetic resonance imaging

INTRODUCTION

Diffusion-weighted MRI (DW-MRI) is a functional MRI technique that quickly provides the degree of diffusion of water molecules within tissues without the use of a contrast agent. In breast imaging, DW-MRI with apparent diffusion coefficient (ADC) values has been used for tumor characterization and the assessment of tumor response after neoadjuvant chemotherapy [1]. Several retrospective studies have investigated its potential for non-contrast

Received: March 31, 2024 **Revised:** April 4, 2024 **Accepted:** April 5, 2024
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breast cancer screening [2,3]. The Diffusion-Weighted MRI Screening Trial (DWIST, NCT03835897), a prospective multicenter study using a standardized protocol for data acquisition and interpretation to compare DW-MRI screening performance with that of mammography, ultrasound, and dynamic contrast-enhanced (DCE) MRI in high-risk women, is being conducted [4].

The background parenchymal signal (BPS) on DW-MRI is the remaining high signal intensity (SI) area within normal breast fibroglandular tissue (FGT) on high b-value images [1,5]. The BPS can affect DW-MRI interpretation similarly as background parenchymal enhancement (BPE) on DCE-MRI, potentially leading to false-negative DW-MRI interpretations in patients with breast cancer [6,7]. Previous research has shown no significant correlation between the menstrual cycle and ADC value of normal breast FGT [8-10]. However, the relationship between the menstrual cycle and BPS is not yet fully understood in healthy premenopausal women. This prospective study aimed to investigate the influence of the menstrual cycle on the BPS and ADC of the breast on DW-MRI in healthy premenopausal women.

MATERIALS AND METHODS

Institutional Review Board of Seoul National University Hospital approved this study (IRB No. 2104-066-1212). Vulnerable participants, including students and employees, were excluded. Informed consent was obtained from all the volunteers.

Study Population

From April to May 2021, seven healthy premenopausal female volunteers (median age, 37 years; range, 33–49 years) with regular menstrual cycles (mean, 31 days; range, 25–42 days) participated in the study. The exclusion criteria are detailed in Supplementary Materials and Methods. Volunteers completed a questionnaire based on medical information and menstrual cycle data of at least 3 months before and during the study (Supplementary Table 1).

Breast MRI Acquisition

All volunteers underwent breast DW-MRI scans four times for each menstrual cycle phase (median interval between adjacent scans, 7 days; range, 4–9 days). ADC maps and synthetic b-values of the 1500 sec/mm^2 (sb1500) images were also obtained from the b-values of the 0 sec/mm^2 (b0), 800 sec/mm^2 (b800), and 1200 sec/mm^2 (b1200) images (see Supplementary Materials and Methods for details).

Visual Assessment of BPS

Three radiologists (B.L.Y., A.J.C., and Y.S.K., with 12, 9, and 2 years of experience in breast imaging, respectively) independently interpreted the images without any supplementary clinical information. BPS was defined as visible SI on high b-value images similar to BPE on DCE-MRI compared to normal FGT on the b0 image [11]. The BPS visual grade was evaluated using a 4-point scale (minimal, mild, moderate, and marked) on the b800, b1200, and sb1500 in axial and maximum intensity projections as previously described (Supplementary Fig. 1) [1]. In cases of asymmetric BPS, grading was based on the more severe side. A consensus on the BPS evaluation was reached considering the majority vote for the main analysis. The amount of FGT was determined by Y.S.K.

BPS Volume (%) Calculation

Y.S.K. segmented the BPS with a semi-automated method using 3D-slicer software (version 4.11; https://www.slicer.org). Each individual's BPS volume (%) was calculated by dividing the total BPS volume on b800 and b1200 by the total FGT volume on b0 (Supplementary Fig. 2). One volunteer with fatty breasts was excluded from semi-automated segmentation because of difficulty in separating normal FGT and fat caused by chemical shift artifacts. Segmentation is not possible in the synthetic image, which calculates the SI with pixel values, because of its noisy nature, making the BPS volume (%) of sb1500 unobtainable.

ADC Measure for BPS and Normal FGT

Y.S.K. measured the ADC values of the BPS (ADC_{BPS}) and normal FGT (ADC_{FGT}) in both breasts using Picture Archiving and Communication System software. To measure the ADC_{BPS}, three regions of interest (ROIs) were drawn for each participant, as large as possible within the areas of high SI with prominent BPS on b1200 images in three different locations. The ADC_{BPS} was then measured on the ADC map by copying and pasting the ROIs from the b1200 images [7]. The ADC_{FGT} was measured for each breast by drawing as large a circular ROI as possible, excluding fat, at the nipple or upper outer quadrant levels, which was repeated three times on the same image for each breast (six measurements per participant) [12]. The mean values of ADC_{BPS} and ADC_{FGT} measurements for each participant were used in the analysis.

Statistical Analysis

Correlation analysis between the visual grade and BPS volume (%) was performed using Spearman's rho test. Agreement in the BPS visual grades among the three radiologists was analyzed using weighted Fleiss kappa. The agreement in ADC_{BPS} measurements among the three locations was assessed using the interclass correlation coefficient (ICC) (single rater, absolute agreement, and two-way mixed model) [13].

Volunteers reported menstrual cycles ranging from 25 to 42 days that were categorized into four phases: early follicular phase (EFP) from 0–5th to 0–14th day, late follicular phase (LFP) from 6–10th to 15–28th day, early luteal phase (ELP) from 11–18th to 29–35th day, and late luteal phase from 19–25th to 36th–42nd day [14,15]. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using MedCalc (version 15.0; MedCalc Software, Ostend, Belgium) and STATA (version 14.0; StataCorp, College Station, TX, USA).

RESULTS

BPS Evaluation: Visual Grade and BPS Volume (%)

For visual grades of BPS on b800, b1200, and sb1500, the Fleiss kappa values for the interobserver reliability were 0.69 (95% confidence interval [CI]: 0.40–0.98), 0.43 (95% CI: 0.31–0.56), and 0.49 (95% CI: 0.24–0.74), respectively. The visual grade of BPS among the seven volunteers ranged from mild to marked on b800 and minimal to moderate on b1200 and sb1500 (Table 1). As the b-value increased, the visual grade of BPS decreased. Among the six volunteers with dense breasts, there was a significant correlation between the visual grade and BPS volume (%) (correlation coefficient, 0.63; $P < 0.001$). The BPS volume (%) was clustered according to the visual grade of BPS (Supplementary Table 2, Supplementary Fig. 3).

Relationship between BPS and Menstrual Cycle

When the BPS was dichotomized as low (minimal to mild) and high (moderate to marked), the rate of high BPS was 92.9% (26/28) and that of low BPS was 7.1% (2/28) on

Table 1. Summary of the consensus visual grade of BPS on high b-value images

Volunteer number	Image	Follicular phase		Luteal phase	
		Early follicular	Late follicular	Early luteal	Late luteal
1	b800	Marked	Marked	Marked	Marked
	b1200	Mild	Mild	Mild	Mild
	sb1500	Minimal	Minimal	Minimal	Minimal
2	b800	Marked	Marked	Marked	Marked
	b1200	Moderate	Moderate	Moderate	Moderate
	sb1500	Mild	Mild	Mild	Mild
3	b800	Marked	Moderate	Marked	Marked
	b1200	Mild	Mild	Minimal	Minimal
	sb1500	Minimal	Minimal	Minimal	Minimal
4	b800	Marked	Marked	Marked	Marked
	b1200	Mild	Mild	Minimal	Mild
	sb1500	Mild	Minimal	Minimal	Minimal
5	b800	Marked	Marked	Marked	Marked
	b1200	Moderate	Moderate	Moderate	Moderate
	sb1500	Mild	Mild	Mild	Mild
6	b800	Marked	Marked	Marked	Marked
	b1200	Moderate	Moderate	Moderate	Moderate
	sb1500	Moderate	Moderate	Moderate	Moderate
7	b800	Marked	Mild	Mild	Moderate
	b1200	Moderate	Mild	Mild	Mild
	sb1500	Mild	Minimal	Minimal	Minimal

The consensus for the visual grade of BPS evaluation was based on the decision when at least two radiologists made the same decision. BPS = background parenchymal signal, b800 = b-value with 800 sec/mm^2 image, b1200 = b-value with 1200 sec/mm^2 image, sb1500 = synthetic b-value with 1500 sec/mm^2 image

 https://doi.org/10.3348/kjr.2023.1189

b800. On the b1200, the rate of high BPS was 46.4% (13/28) and that of low BPS was 53.6% (15/28). In contrast, on sb1500, the rate of high BPS was 14.3% (4/28) and that of low BPS was 85.7% (24/28). Four women (57.1%) showed no change in the visual grade of the BPS on b800, b1200, and sb1500 according to the menstrual cycle. Three women (42.9%) showed changes in visual grade during the menstrual cycle on different b-value images. Two had the highest visual grade in the EFP and the lowest visual grade in the LFP on b800. All volunteers showed the highest visual grade in the EFP on b1200. Two of them showed the highest visual grade in the EFP on sb1500. However, the variation was confined to two grades, except for one volunteer with fatty breasts who changed from marked BPS to mild BPS on b800 (Supplementary Fig. 4). Volunteers with or without parity and lactation history were not associated with the presence or absence of BPS visual grade changes during all menstrual cycles. The BPS volume (%) on b800 and b1200 showed the highest value in 50% (3/6) of volunteers with dense breasts in the EFP (Fig. 1).

ADC Values of BPS and Normal Fibroglandular Tissue

The mean ROI size of ADC_{BPS} was 7.85 ± 3.39 mm^2 (range, 3.81–20.19 mm^2) and that of ADC_{FGT} was 193.53 ± 48.01 mm^2 (range, 55.13–209.50 mm^2). The ICC for the ADC_{BPS} was 0.625 (95% CI, 0.31–0.81). The mean ADC_{BPS} and ADC_{FGT} were 1.51 ± 0.15 x 10^{-3} mm^2/sec (95% CI: 1.45–1.56) and 1.87 ± 0.30 x 10^{-3} mm^2/sec (95% CI, 1.76–1.99), respectively. Three of the seven volunteers (42.9%) showed the lowest ADC_{BPS} in the EFP, four (57.1%) showed the highest ADC_{BPS} in the ELP. Additionally, four (57.1%) showed the lowest ADC_{FGT} in the LFP, but the variation was very small (Fig. 2).

DISCUSSION

Recently, interest in DW-MRI as a non-contrast breast cancer screening tool has grown. It is recommended that BPS levels be included in the interpretation of DW-MRI [3,4]. This study evaluated whether the BPS and ADC were influenced by the menstrual cycle in healthy women. Most volunteers did not exhibit specific patterns; however, some trends were observed. The highest BPS was frequently observed in the EFP. For ADC_{BPS}, the lowest values were more frequently observed in the EFP and the highest in the ELP. BPE levels are higher later in the menstrual cycle [16-20]. However, the BPS during the menstrual cycle has not been studied in healthy premenopausal women. Previous studies indicated that the detectability of invasive ductal carcinoma on DW-MRI was not affected by the menstrual cycle [12]. However, they only included cancers > 1 cm in size, and the images used were not suitable for breast cancer screening. Reports vary regarding the effect of the menstrual cycle on the ADC value of FGT. Some studies [8-10] reported no change in the ADC during menstrual cycles, whereas others showed a lower ADC in the follicular phase than in the luteal phase [21,22]. The decrease in ADC_{FGT} in the LFP in this study was consistent with the results of other studies [9,22]. The changes in BPS

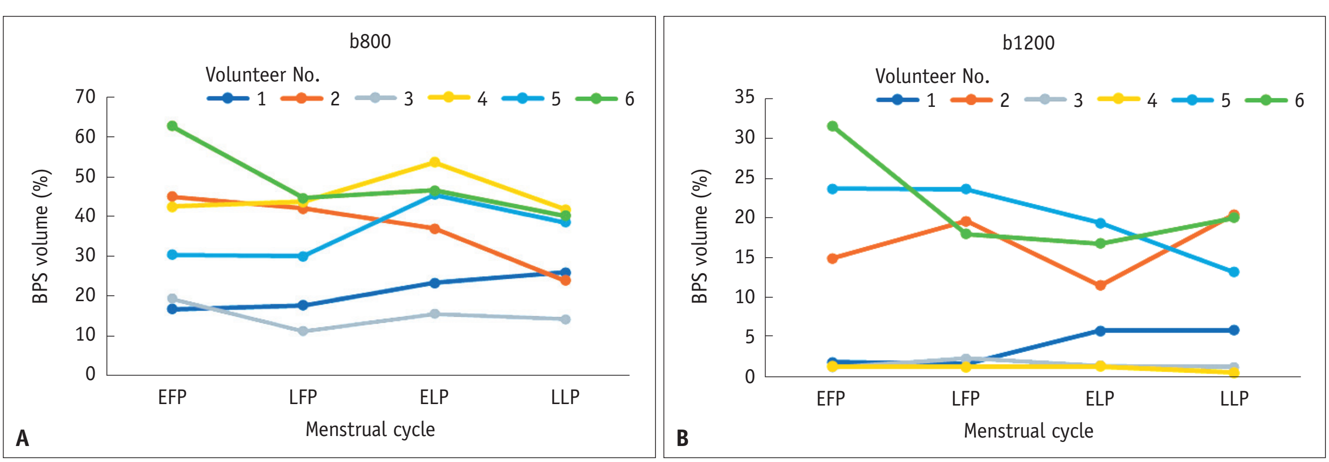

Fig. 1. Changes in the BPS volume (%) in **(A)** b800 and in **(B)** b1200 diffusion-weighted MRI with respect to the menstrual cycle. The plot shows the changes in BPS volume (%) in the b800 and b1200 of six volunteers with dense breasts according to their menstrual cycle. The BPS volumes (%) of volunteers 2, 3, and 6 in b800 and volunteers 4, 5, and 6 in b1200 were highest during the EFP. BPS = background parenchymal signal, b800 = b-value with 800 sec/mm^2 image, b1200 = b-value with 1200 sec/mm^2 image, EFP = early follicular phase, LFP = late follicular phase, ELP = early luteal phase, LLP = late luteal phase

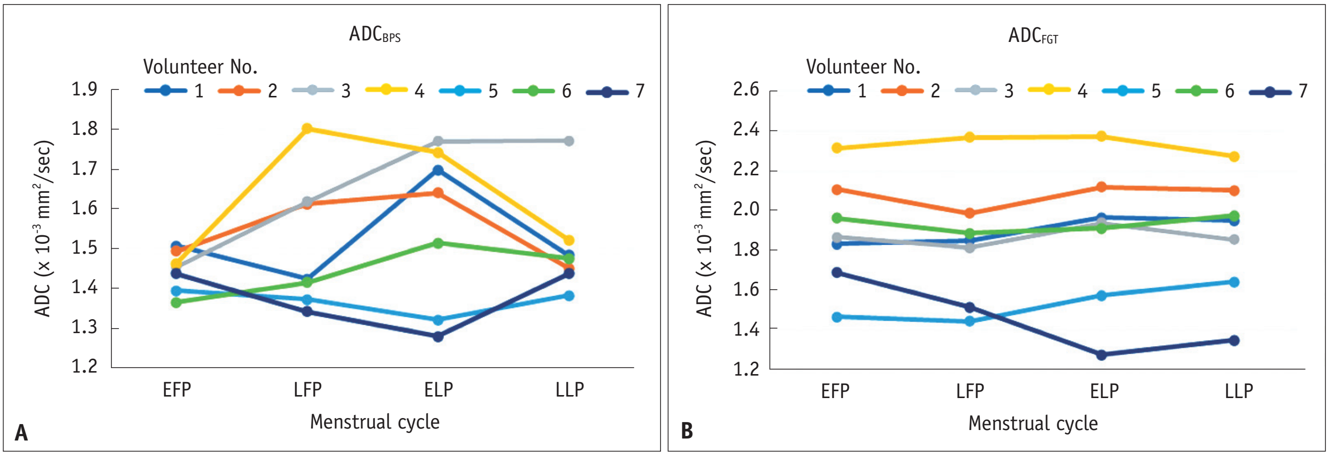

Fig. 2. Changes in the ADC_{BPS} **(A)** and the ADC_{FGT} **(B)** with respect to the menstrual cycle. **A:** Plot of ADC_{BPS} shows that three of seven volunteers showed the lowest ADC_{BPS} in the EFP. **B:** Plot of ADC_{FGT} shows that four of seven volunteers showed the lowest ADC_{FGT} in the LFP. ADC = apparent diffusion coefficient, BPS = background parenchymal signal, FGT = fibroglandular tissue, EFP = early follicular phase, LFP = late follicular phase, ELP = early luteal phase, LLP = late luteal phase

and ADC during the menstrual cycle were not significant enough to draw a definitive conclusion. Therefore, further studies with larger sample sizes are warranted.

The etiology of BPS remains unclear. In our study, BPS grade was not related to body mass index, parity, or lactation history. As DW-MRI reflects water molecule diffusion influenced by the surrounding microstructure, differences in physiological and biochemical compositions between individuals can be reflected in the BPS. The follicular phase is characterized by a dense stroma and high proliferative activity, whereas the luteal phase shows stromal edema, ductal distension with secretion, and venous congestion [23]. In addition, we observed a decrease in ADC_{BPS} in the EFP. The mean ADC_{BPS} was lower than the mean ADC_{FGT} for each patient. The ROI of the ADC_{BPS} was located at a relatively peripheral region compared with the ROI of the ADC_{FGT}. In the ex vivo study, the mean diffusivity increased in the order of the gland lobule, stroma, and lumen. The relatively large number of lumens at the nipple level of the breast could be the cause of the difference in ADC values between BPS and FGT [24]. The composition of the gland lobule, stroma, and lumen could potentially be the cause of the different lowest ADC timings between BPS and FGT during the menstrual cycle. Furthermore, various benign conditions, such as fibroadenoma, cysts, and fibrocystic disease, showed intermediate SI on DW-MRI [7]. Some BPS may have originated from these lesions. Future studies should determine whether BPS levels are related to the risk of breast cancer in healthy women or to the prognosis of patients with breast cancer.

The evaluation of women with a high BPS is challenging because a higher b-value lowers the BPS grade. Among all volunteers, the proportion of high BPS decreased from 92.9% on b800 to 46.4% on b1200. However, half of the volunteers still had a high BPS on b1200, whereas only one volunteer showed a high BPS on sb1500. Synthetic high-b-value DW-MRI, such as sb1500, may improve tumor-to-tissue contrast, lesion visibility, and image quality, and help interpret DW-MRI [25-27].

This study has several limitations. First, the small number of volunteers, which resulted from the need for repeated examinations in healthy volunteers, hindered the formal statistical analysis. Second, previous studies assessing menstrual cycle changes often used fixed one-week intervals, not accounting for variability in the length of each phase among individuals. The examination intervals were adjusted based on each participant's menstrual phases, reflecting their unique physiology [28]. Third, most volunteers had dense breasts. Fatty breasts were excluded from the semi-automatic segmentation analysis because of strenuous chemical shift artifacts. Therefore, the results may not be generalizable. Despite this limitation, focusing on dense breasts provides promising insights into the use of DW-MRI for breast cancer screening in women with dense breasts.

Most volunteers did not exhibit specific BPS patterns during their menstrual cycles. However, the highest BPS and lowest ADC_{BPS} were more frequently observed in the EFP than in the other phases of the menstrual cycle, while the highest ADC_{BPS} was more common in the ELP. The lowest ADC_{FGT} was more frequently observed in the LFP. Further studies are required to assess whether BPS assessment can provide valuable information for breast cancer diagnosis and risk assessment.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2023.1189.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Yeon Soo Kim, Bo La Yun, Woo Kyung Moon, Sun Mi Kim. Data curation: Yeon Soo Kim, Bo La Yun. Formal analysis: Yeon Soo Kim, Bo La Yun, Hee Jung Shin. Investigation: Yeon Soo Kim, Bo La Yun, A Jung Chu, Su Hyun Lee, Hee Jung Shin. Methodology: Yeon Soo Kim, Bo La Yun, Woo Kyung Moon, Sung Ui Shin, Mijung Jang. Project administration: Yeon Soo Kim, Bo La Yun, Woo Kyung Moon. Resources: Yeon Soo Kim, Bo La Yun, A Jung Chu, Su Hyun Lee. Software: Yeon Soo Kim, Bo La Yun, Hee Jung Shin. Supervision: Bo La Yun, Woo Kyung Moon. Validation: Yeon Soo Kim, Bo La Yun, Woo Kyung Moon. Visualization: Yeon Soo Kim, Bo La Yun, Woo Kyung Moon. Writing—original draft: Yeon Soo Kim, Bo La Yun, Woo Kyung Moon. Writing—review & editing: all authors.

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Funding Statement

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. NRF-2019R1F1A1062646) and Research Program 2021 funded by Seoul National University College of Medicine Research Foundation.

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