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Diffusion-weighted MRI: Association between patient characteristics and apparent diffusion coefficients of normal breast fibroglandular tissue at 3 tesla

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Abstract

OBJECTIVE—To assess associations between patient characteristics and apparent diffusion coefficient (ADC) values of normal breast fibroglandular tissue on diffusion-weighted imaging (DWI) at 3 tesla.

MATERIALS and METHODS—The retrospective study included 103 women with negative bilateral findings on 3T breast MR examinations (BI-RADS 1). DWI was acquired during clinical breast MRI scans using $b = 0, 800 \text{ s/mm}^2$. Mean ADC of normal breast fibroglandular tissue was calculated for each breast using a semi-automated software tool in which parenchyma pixels were selected by interactive thresholding of the $b=0 \text{ s/mm}^2$ image to exclude fat. Intrasubject right and left breast ADC values were compared and averaged together to evaluate the association of mean breast ADC with age, mammographic breast density and background parenchymal enhancement (BPE).

RESULTS—Overall mean breast ADC was $1.62 \pm 0.30 \times 10^{-3} \text{ mm}^2/\text{s}$. Intrasubject right and left breast ADC measurements were highly correlated ($R^2=0.89$, $p<0.0001$). Increased breast density was strongly associated with increased ADC ($p<0.0001$). Age and BPE were not associated with ADC.

CONCLUSION—Normal breast parenchymal ADC values increase with mammographic density, but are independent of age and BPE. Since breast malignancies have been shown to have low ADC values, DWI may be particularly valuable in women with dense breasts due to greater lesion to normal tissue contrast.

Introduction

Diffusion-weighted imaging (DWI) is a short (2–3 minutes) non-contrast MRI technique that has shown promise for the detection and characterization of breast cancer. DWI measures the three dimensional mobility of water in tissues and is sensitive to microstructural properties including cell density, cellular organization, and cell membrane

integrity. Diffusion can be quantified by using the apparent diffusion coefficient (ADC) to increase the specificity of this technique [1]. Cellular density is increased in malignancies, which is reflected by lower ADC [2–6]. Within the past fifteen years, there have been approximately 100 publications investigating the role of DWI in the breast. These studies have largely focused on using DWI to distinguish between benign and malignant lesions or monitor response of a known cancer to treatment and have demonstrated potential for DWI to detect and characterize breast malignancies [7].

Despite a large amount of scientific research and published data, clinical use of DWI is still not widespread. This is likely due to the lack of standardization of DWI parameters and a uniform method of interpretation. The development of standardized interpretation criteria requires a solid understanding of the appearance and normative range of ADC values of the normal breast on diffusion imaging. However, only a small fraction of the DWI publications have specifically focused on characterizing the normal breast [8–13].

Breast ADC can vary widely between individuals and different baseline ADC values may affect the conspicuity of malignancy. Improved understanding of factors influencing ADC in normal breast tissue is needed to simplify and standardize interpretation of diffusion images. The purpose of this study was to measure ADC values in normal breast tissue at 3 tesla (T) and assess whether they correlate with patient characteristics of age, breast density, and/or background parenchymal enhancement.

Materials and Methods

Subjects

This Health Insurance Portability and Accountability Act-compliant study was approved by the Institutional Review Board. Consecutive screening breast MR examinations performed from February 2010 to March 2011 were retrospectively reviewed. Informed consent was waived due to the retrospective nature of the study. DWI was performed as part of the standard clinical protocol over this timeframe. Eligible subjects were those with a bilateral negative screening breast MRI (ACR Breast Imaging Reporting and Data System (BI-RADS) assessment of 1) and a negative or benign screening mammogram (ACR BI-RADS assessments of 1 or 2) [14]. There were 130 consecutive women identified over the study timeframe who met the inclusion criteria. DWI was not performed in the clinical MRI examination for 21 of 130 women (16%) due to time constraints at the time of imaging. Five of 109 women with DWI were excluded from the study because mammograms were not performed or not available for review, and one subject was excluded who had a congenital abnormality leading to markedly asymmetric breast size. Therefore, 103 women were included in the final study cohort (Table 1). The mean subject age was 47 ± 11 years.

Magnetic resonance imaging acquisition

In our high risk screening MRI population, DWI was obtained as part of the standard clinical breast MRI acquisition on a 3T Philips Achieva scanner (Philips Healthcare Best, The Netherlands) using a 16-channel breast coil. The clinical breast MRI protocol also included a T2-weighted fast spin echo sequence, T1-weighted non-fat suppressed sequence,

and a T1-weighted fat-suppressed dynamic contrast-enhanced (DCE) MRI sequence. DWI was performed following the DCE MRI acquisition, which is considered to be the most critical part of the examination, in case a patient was not able to tolerate the entire examination due to claustrophobia or other discomfort. DWI was acquired using a diffusion-weighted echo planar imaging sequence with parallel imaging array spatial sensitivity encoding technique (ASSET); reduction factor =3, repetition time/echo time = 5336/61 msec, 2 averages, matrix = 240×240 , field of view = 36 cm, slice thickness = 5 mm, and gap = 0. Diffusion gradients were applied in six directions with $b = 0$ and 800 sec/mm^2 .

Image analysis

The MR examinations were interpreted prospectively by one of four fellowship trained radiologists specializing in breast imaging. Each case was reviewed for suspicious features and characterized using the American College of Radiology BI-RADS Breast MRI Lexicon. Additional features of each examination were recorded at the time of interpretation including assessment of background parenchymal enhancement (BPE) and mammographic breast density. This information was entered into our institutional University of Washington Seattle Cancer Care Alliance Breast Imaging Database [15] and extracted for this study.

The diffusion-weighted images were retrospectively analyzed by a radiologist (JS) who was blinded to patient characteristics in the medical record (age, mammographic breast density, BPE classification), but was not blinded to the DCE and other MR images acquired during the same examination. Diffusion maps were created using Java-based image processing software incorporating ImageJ (National Institutes of Health, public domain). ADC maps were calculated from the spatially registered diffusion-weighted images by

$$\text{ADC} = (-1/b) \ln (S_{\text{DWI}}/S_0) \quad [1]$$

where S_{DWI} is the combined DWI (geometric average of individual $b = 800 \text{ sec/mm}^2$ diffusion-weighted images), and S_0 is the T2-weighted $b = 0 \text{ sec/mm}^2$ reference image [16].

Mean ADC of normal breast fibroglandular tissue was calculated for each breast using a semi-automated software tool in which parenchyma pixels were selected by interactive thresholding of the $b=0$ image to exclude fat. A region of interest (ROI) was defined on the threshold image at the level of the nipple for each breast to include the entire breast fibroglandular tissue, excluding the fat (Figure 1). In the case of a cyst identified in the slice of interest, the ROI was drawn to avoid the cyst or an alternate nearby slice outside the cyst was chosen. The breast parenchymal ADC was calculated as the mean of the voxels in the ROI.

Patient Characteristics

Patient characteristics were recorded from the medical record. In the radiological reports, mammographic density was categorized at the time of interpretation as either fatty, scattered fibroglandular tissue, heterogeneously dense or extremely dense (in increasing order). Each breast was given a density assessment and the highest assessment was used. One hundred two of 103 women had the same density level given for both breasts. Background

parenchymal enhancement on DCE MRI was categorized as minimal, mild, moderate or marked (in increasing order). Each breast was given a BPE assessment and the highest assessment was used. One hundred two of 103 women had the same BPE level given for both breasts. The instances of differing bilateral density and BPE assessments were in two different women.

Statistical Analyses

Intrasubject right and left breast ADC values were compared by Pearson's correlation coefficient, and were then averaged together for comparison of mean breast ADC with subject age (<50 versus ≥50 years), breast density (fatty or scattered fibroglandular tissue versus heterogeneously or extremely dense) and BPE (minimal or mild versus moderate or marked). Single variable linear regression was conducted to determine variation of ADC across characteristics of interest. Multivariable linear regression was performed to identify independent predictors. All analyses were performed using SAS statistical software, version 9.3 (SAS Institute, Cary, NC).

Results

Patient characteristics are given in Table 1. Overall mean breast ADC was $1.62 \pm 0.30 \times 10^{-3} \text{ mm}^2/\text{sec}$ (N= 103). Intrasubject right and left breast ADC measurements were highly correlated ($R^2=0.89$, $p<0.0001$), with mean absolute difference of $0.08 \pm 0.06 \times 10^{-3} \text{ mm}^2/\text{sec}$ (5.5%) (Figure 2). Therefore, further analyses were conducted at the level of the subject rather than the breast.

Single Variable Analyses

Increased mammographic breast density, was associated with higher ADC when compared to decreased mammographic breast density, 1.70 ± 0.28 vs. 1.42 ± 0.28 , $p<0.0001$. There was no association between minimal and mild BPE versus moderate and marked BPE; ADC of 1.60 ± 0.33 vs. 1.66 ± 0.24 , respectively, $p = 0.33$. Further comparison of extreme categories of minimal versus marked BPE also did not demonstrate any difference in ADC ($p=0.61$). The women in the younger age group (<50 years) demonstrated higher ADC when compared to the older age group (≥50 years) (1.67 ± 0.29 vs. 1.56 ± 0.31 , $p = 0.05$).

Multivariable Analysis

Breast density is increased in younger women, so multivariable linear regression was used to evaluate the independent effects of age and density on ADC (interaction assessment). Although differences in ADC values by age groups was significant by univariate analysis, it was not significant in multivariable analysis when controlling for density ($p=0.11$). Increased breast density was highly associated with increased ADC ($p<0.0001$) (Table 2). Imaging examples from a woman with low breast density and low ADC and a woman with high breast density and high ADC are provided in Figures 3 and 4.

Discussion

Our study stratified normal tissue ADC values by patient characteristics of density, age and BPE and found ADC to be highly associated with breast density but not with age or BPE. Breast ADC can vary widely between normal individuals, so improved understanding of factors influencing ADC measurements in normal breast tissue is needed for practice standardization. Prior to this study, there were several smaller studies that established a normative range of breast ADC values [3, 6, 8, 10–13, 17]. One of those earlier studies reported that ADC values were inversely associated with age; however, breast density was not included in their analysis [12].

Women with dense and extremely dense breasts are at increased risk for breast cancer [18, 19]. Unfortunately, the sensitivity of mammography to detect malignancy is also reduced in this population [20, 21]. DWI is a non-contrast, safe, rapid imaging tool that can potentially be used as an adjunct to mammography. Breast malignancies can be detected on DWI by low diffusivity and low ADC. Our data suggest that DWI may be especially useful in women with dense breasts since their baseline ADC values are relatively high, which should increase the conspicuity of malignancy as in the example shown in Figure 5. Previous work demonstrated that inadequate fat suppression can cause underestimation of the ADC [17]. Since it is impossible to suppress all fat signal, the higher background ADC in dense breasts may be due to less intravoxel partial-volume averaging with fat that is not fully suppressed.

Increased BPE on breast MRI is associated with a higher abnormal interpretation rate without affecting sensitivity for cancer detection [22, 23]. DWI has potential to improve the diagnostic performance of DCE MRI [24–27] and might be especially useful to increase specificity in cases with increased BPE. Since BPE varies with timing of the menstrual cycle [28, 29], many centers require pre-menopausal patients to time screening DCE MRI examinations to certain days in the cycle. To our knowledge, ours is the first study demonstrating that BPE is not associated with variations in normal parenchymal ADC. This finding is in agreement with previous studies demonstrating no significant menstrual cycle variation of ADC measurements in the normal breast [10, 13].

Our study has several limitations. First, it is a retrospective cohort study, which by design cannot establish causal relationships, but is intended to assess associations. Another limitation is that our pre-menopausal screening MRI examinations were generally timed in the women's menstrual cycles to minimize BPE. Thus, it is possible that an association between ADC and BPE could have been missed because of decreased range of BPE. However, nearly one third of our subjects had BPE that was moderate or marked, suggesting considerable variation of BPE in the range of our study sample and thus decreasing the possibility of missing a significant association between ADC and BPE because of BPE range restriction. Finally, approximately two thirds of the women in our study cohort had breast density in the upper two density quartiles. In the general population, about half of women are in the upper two density quartiles [30]. However, our data, which was in a high risk screening population, reflects the population of high risk women with dense breasts for which DWI should add the most information to the screening process.

Future directions will include using knowledge of normal baseline ADC values to develop a standardized quantitative approach to interpreting DWI for the identification and characterization of breast lesions. This will facilitate multi-center clinical trials to evaluate the potential of this tool for screening, especially in women with dense breasts.

In summary, this study offers improved understanding of patient characteristics associated with ADC in normal breast tissue. Specifically, normal breast parenchymal ADC values are independent of BPE and age and are higher in those with greater mammographic density. Recently, several states have passed legislation mandating that women have a right to know if their breast density is increased. Unfortunately, there are no clear guidelines as to what women should do with this information and which, if any, additional screening exams might be helpful. Given that the sensitivity of mammography for cancer detection decreases as breast density increases, DWI has the potential to complement mammography as a screening tool for cancer detection. High normal tissue ADC values may accentuate the conspicuity of malignancies on DWI, which could be especially important in the higher risk population of women with dense breasts.

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Fig. 1.

Example of the semi-automated DWI analysis. Mean ADC of normal breast fibroglandular tissue was calculated for each breast using a semi-automated software tool in which fibroglandular tissue pixels were selected by interactive thresholding of the $b=0$ image to exclude fat. An ROI was defined on the threshold image for each breast to include the entire breast parenchyma, excluding the fat.

(a) Diffusion-weighted image ($b=0$) at the level of the nipple used for analysis, prior to thresholding.

(b) Thresholded $b=0$ image with a circular outline over the right breast defining the ROI for this breast.

Fig. 2. Intrасubject comparison of left and right breast ADC measures in 103 subjects with negative breast MRI examinations (BI-RADS 1).

Fig. 3. 52 year old female with known BRCA2 mutation underwent breast MRI for high risk screening. The subject was classified as having low breast density on mammography (a) and minimal BPE on DCE MRI (b). Axial MR images are shown at the level of the nipple (c–e). (a) MLO view mammogram demonstrating scattered fibroglandular densities in a normal breast. (b) Post-contrast subtraction maximum intensity projection (MIP) demonstrating minimal BPE. (c) Post-contrast T1-weighted (T1W) image. (d) DW MRI $b=0 \text{ s/mm}^2$ T2-weighted image. (e) ADC map (mean $\text{ADC} = 1.23 \times 10^{-3} \text{ mm}^2/\text{sec}$).

Fig. 4.

26 year old female with a strong family history of breast cancer underwent breast MRI for high risk screening. The subject was classified as having high breast density on mammography (a) and marked BPE on DCE MRI (b). Axial MR images are shown at the level of the nipple (c–e).

(a) MLO view mammogram demonstrating extremely dense fibroglandular tissue in a normal breast.

(b) Post-contrast subtraction MIP demonstrating marked BPE.

(c) Post-contrast T1W image.

(d) DW MRI $b=0 \text{ s/mm}^2$ T2-weighted image.

(e) ADC map (mean $\text{ADC} = 2.0 \times 10^{-3} \text{ mm}^2/\text{sec}$).

Fig. 5.

47 year old female with biopsy proven DCIS from screen detected calcifications. An MRI was done for extent of disease and a mammographically occult mass was identified. This was given a BI-RADS 4, suspicious assessment code. Subsequent biopsy yielded invasive ductal carcinoma. The subject was classified as having extremely high breast density on mammography (a). Axial MR images are shown at the level of the nipple (b–e). The mass is not visible on the mammogram and is marked with an arrow on the MRI.

(a) ML view mammogram demonstrating extremely dense fibroglandular tissue. There is a biopsy clip at 6:00 representing known DCIS.

(b) Post-contrast subtraction MIP demonstrating moderate BPE.

(c) Post-contrast T1W image.

(d) DW MRI $b=800 \text{ s/mm}^2$ T2-weighted image.

(e) ADC map (mean ADC of the malignancy= $1.0 \times 10^{-3} \text{ mm}^2/\text{sec}$).

Table 1

Patient characteristics.

	Groups	N (%)
Breast Density	Fatty	3 (2.9%)
	Scattered Heterogeneous	26 (25.2%)
	Heterogeneously Dense	52 (50.5%)
	Extremely Dense	22 (21.4%)
BPE	Minimal	39 (37.9%)
	Mild	32 (31.1%)
	Moderate	17 (16.5%)
	Marked	15 (14.6%)
Age	<50	56 (54.4%)
	50	47 (45.6%)

Table 2

Comparison of ADC by patient characteristics.

	Patient Characteristics	N	Mean ADC $\pm$ SD ($\times 10^{-3}$ mm ² /sec)	Univariate Linear Regression (p)	Multivariate Linear Regression
Overall		103	1.62 $\pm$ 0.30		
Age	<50	56	1.67 $\pm$ 0.29	0.05	0.11
	50	47	1.56 $\pm$ 0.31		
Breast density	Fatty Scattered	29	1.42 $\pm$ 0.28	<0.0001	<0.0001
	Heterogeneously dense Extremely dense	74	1.70 $\pm$ 0.28		
BPE	Minimal, Mild	71	1.60 $\pm$ 0.33	0.33	0.89
	Moderate, Marked	32	1.66 $\pm$ 0.24		