Study of the characteristics of Normal Breast Tissue during Various Phases of Menstrual Cycle by in vivo Volume Localized Proton MR Spectroscopy (MRS)

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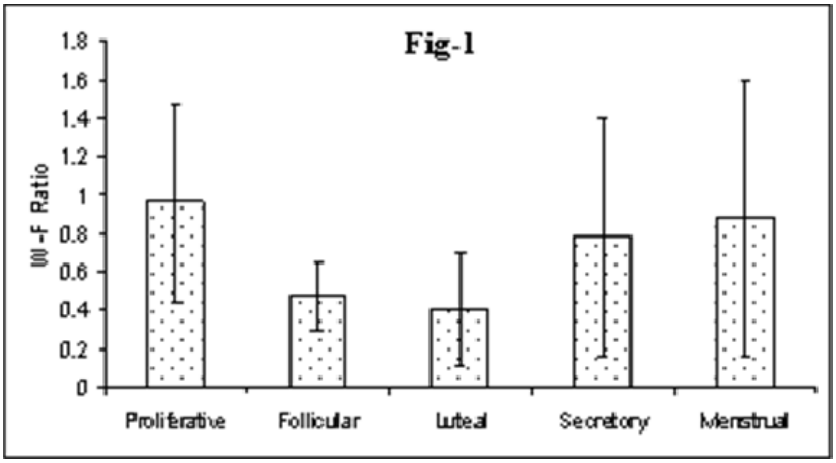
OBJECTIVE: To evaluate the variation of the water-fat (W-F) ratio of the normal breast tissue of female volunteers as a function of the various histological phases of the menstrual cycle using sequential *in vivo* proton (^{1}H) MR spectroscopy.

INTRODUCTION: Breast tissue shows high proliferative activity and histological changes throughout the menstrual cycle (1). These changes contribute to the heterogeneity of breast that may influence the detection of breast disease. Thus, it is important to understand the changes in biochemistry, function, heterogeneity as well as the influence of hormonal variation during various phases of menstrual cycle before identifying the changes related to malignant transformation. *In vivo* MRS has been used for the characterization of breast lesions using information of the cellular chemistry as well as water to fat (W-F) ratio. MRS studies have shown that neoplastic breast tissues contain higher water content compared to normal tissues and the (W-F) ratio can be used for diagnosis (2,3). Further, reduction of W-F has been shown to serve as a noninvasive response indicator to monitor tumor response (4). Dzendrowskyj *et al* reported cyclic variations of the lipid content throughout the menstrual cycle in normal breast tissue using *in vivo* MR spectroscopy (5). It was reported that alterations in lipid concentrations and lipase activity accompany the breast disease (6). Thus, the objectives of the present study were: (a) to investigate the MR spectral characteristics and the estimation of W-F ratio using volume localized *in vivo* ^{1}H MRS from different regions of the normal breast of volunteers in relation to the heterogeneous nature of the breast tissue, and (b) to understand the influence of various histological phases of menstrual cycle on the W-F ratio from the three different regions of the normal breast.

MATERIALS AND METHODOLOGY: Twenty-four healthy pre-menopausal female volunteers [average age = 34.2 ± 6.0 years (range, 26-43); non-pregnant and non-lactating)] were recruited for this study. The Institute ethical committee approved the study and informed consent was obtained from each subject. ^{1}H MRS was carried out at 1.5 T (Magnetom 63 SP/Avanto, Siemens) using a dedicated bilateral breast coil with the body coil as the transmitter. A PRESS sequence with a voxel size of 2 x 2 x 2 cc from 3 different regions of the breast namely: the para-areolar region, the upper and/or the lower quadrants were used. A total of 121 MR spectroscopic examinations were carried out on 24 volunteers. Of these, 37 MRS examinations were performed in 17 volunteers who were monitored at only one time point (days ranging from 2 to 30). The remaining 84 MR examinations were carried out on seven volunteers, monitored sequentially at four time points with the interval of 6-7 days comprising five histological phases of the menstrual cycle in all 3 regions.

Menstrual Phases	W-F value from different regions of the breast of normal volunteers			p-value
	Lower (a)	Para-areolar (b)	Upper (c)	
Proliferative phase	0.23±0.13	0.96±0.51	0.27±0.16	0.0001 with (b, c) & 0.78 with (a)
Follicular phase	0.29±0.19	0.47±0.18	0.29±0.20	0.09 with(b), 0.1with (c) & 0.9 with (a)
Luteal phase	0.26±0.18	0.40±0.29	0.17±0.12	0.2with(b) 0.05,with (c) & 0.4 with (a)
Secretory phase	0.31±0.08	0.77±0.62	0.23±0.11	0.02 with (b), 0.006 with (c) & 0.6 with (a)
Menstrual phase	0.33±0.37	0.87±0.71	0.49±0.60	0.13 with (b), 0.33 with (c) &0.67with(a)



RESULTS: The W-F values calculated for the three regions of the breast during the various phases of the menstrual cycle [proliferative (days 3-7), follicular (days 8-14), luteal (days 15-20), secretory (21-27), and menstrual phases (days 28-2)] are presented in Table-1. The variation of W-F value of the para-areolar region during the various phases of the menstrual cycle is shown in Figure 1. A W-F value of 0.96 ± 0.5 was observed during the proliferative phase which reduced to 0.47 ± 0.18 and 0.40 ± 0.29 during follicular and luteal phases, respectively. The value increased to 0.77 ± 0.6 during secretory and to 0.87 ± 0.7 during the menstrual phases. No significant difference was observed in the W-F value for upper and the lower quadrants of the breast. However, W-F ratio of the para-areolar region was significantly higher compared to the upper and the lower quadrants especially during proliferative and secretory phases.

DISCUSSION: In the MR spectrum of the para-areolar region, the water peak dominates with much lower contribution from fat and is different from the upper and lower quadrants of the breast where lipid peak dominates. Elevated W-F value of para-areolar region is due to the high percentage of the water present in ducts and in glandular lobules. Both upper and lower quadrants are composed mainly of adipose tissue with less number of lobules, hence a lower W-F ratio was observed. Further, W-F value of para-areolar region was high in the proliferative phase indicating lower lipid content. The value was low during follicular and luteal phases suggesting an increase in the lipid content. A gradual increase of the W-F value was observed during secretory and menstrual phases; indicating cyclic changes of the W-F ratio during menstrual cycle (see Figure 1). Graham *et al* observed similar cyclic changes in the breast parenchyma during menstrual cycle using mean relative water content and fibroglandular fraction using MRI (7). Both the parameters were found to be elevated during menstrual period and reduced during the mid cycle. Cyclic changes reported in lipid content during menstrual cycle further corroborate our results (5). W-F values for the upper and lower quadrants showed no significant changes, implying that hormone-associated changes due to menstrual cycle have little effect in upper and lower quadrants of the breast. The present study demonstrated the potential of ^{1}H MRS to monitor changes in the breast tissue characteristics due to physiological factors like menstrual cycle. Further, any assessment of the breast pathology (e.g. tumor) using W-F ratio have to be carried out taking into consideration the location of the tumor within the breast as well as the time of menstruation.

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