Diffusion Tensor Imaging of the Breast: Hormonal Regulation

Noam Nissan[1], Edna Furman-Haran[2], Myra Shapiro-Feinberg[3], Dov Grobgeld[1], and Hadassa Degani[1]

[1]*Department of Biological Regulation, Weizmann Institute of Science, Rehovot, Israel,* [2]*Unit of Biological Services, Weizmann Institute of Science, Israel,* [3]*Meir Medical Center, Kfar Saba, Israel*

Purpose: To investigate the hormonal regulation of breast diffusion tensor imaging (DTI) throughout the menstrual cycle phases, during lactation and in post-menopause with and without hormonal replacement therapy (HRT).

Introduction: Dynamic contrast enhanced (DCE) is the current clinical protocol applied for breast MRI. However, hormonal induced changes in the normal breast parenchymal enhancement may influence the accuracy of breast cancer diagnosis (1). Hence, in premenopausal women the recommended examination period is limited to days 6-16 of the menstrual cycle, and in postmenopausal women under hormonal replacement therapy (HRT) treatment should be discontinue for at least four weeks. In addition DCE is not recommended during pregnancy and in lactating women it's utility is limited (2). Diffusion tensor imaging (DTI) uses a none-invasive MRI protocol which extends the ability of diffusion measurements to investigate microstructural features in addition to cellular density. Recently DTI studies of the normal breast (3,5-6) and of breast lesions (4-7) reported lower values of ADC in cancers, as well as of the first principal diffusion coefficient (λ1) and the maximum anisotropy index (λ1-λ3) (5-6), as compared to normal breast tissue and to benign lesions. The results demonstrated the ability of the DTI parameters to detect and diagnose breast cancer. This research was aimed to find out whether the DTI diffusion parameters are affected by hormonal changes in pre and post-menopausal women. Thus far hormonal induced changes in diffusion parameters were investigated only by preliminary DWI studies, yielding conflicting results (8-10).

Methods: 45 healthy volunteers were scanned using T2-weighted and DTI sequences at 3T, using the diffusion gradients in 30 directions during 5 minutes, b-values of 0 and 700 s/mm^2, TE/TR of 120/10400 ms, and resolution of 1.9×1.9×2.5mm^3. Pre-menopausal volunteers (n=16) were weekly scanned four times during one menstrual cycle. Post-menopausal volunteers (n=19) and lactating volunteers (n=10) were scanned once. The principal diffusion coefficients (λ1, λ2, λ3), apparent diffusion coefficient (ADC), fractional anisotropy (FA), and maximal anisotropy (λ1- λ3) were calculated pixel-by-pixel for the entire breast fibro-glandular tissue.

Results: In all premenopausal volunteers the diffusion tensor parameters exhibited high repeatability, remaining almost equal along the menstrual cycle (see Figure 1 showing λ1 values), with a low mean within subject Coefficient of Variance of λ1, λ2, λ3, ADC (1-2%), and FA (5%), as well as a high intra-class correlation (0.92-0.98). Parametric DTI maps and the corresponding histograms of the parameters (figure 1a) demonstrated similarity in the spatial and histogram distribution of the parameters. Comparison between the premenopausal groups with and without oral contraceptives (OCs) did not show any statistically significant differences for all DTI parameters (p=0.28-0.82).

The diffusion coefficients were significantly lower in the post-menopausal HRT (-) as compared to the HRT (+) ($p<0.01$) or to the premenopausal volunteers ($p<0.01$), while no significant differences in all DTI parameters were found between pre-menopausal and post-menopausal HRT (+) volunteers (p=0.31-0.93). In comparison to the non-lactating premenopausal volunteers, the lactating breast diffusion coefficient values were significantly lower by 13-21% ($p<0.005$), although FA remained similar. This decline was not related to the extent of fibro-glandular tissue, since the percentage of fibro-glandular tissue in the two groups was not significantly different (p=0.83). We, therefore, suggest that the higher viscosity of the milk in the lactating breast, relative to the viscosity of the normal breast water milieu is responsible for the slower diffusion coefficients. The diffusion vector map and diffusion coefficient, maps of the lactating breast are illustrated in Fig 2, showing directional diffusion along the anterior-posterior axis, reflecting the structure of milk ducts heading from the base of the breast towards the nipple.

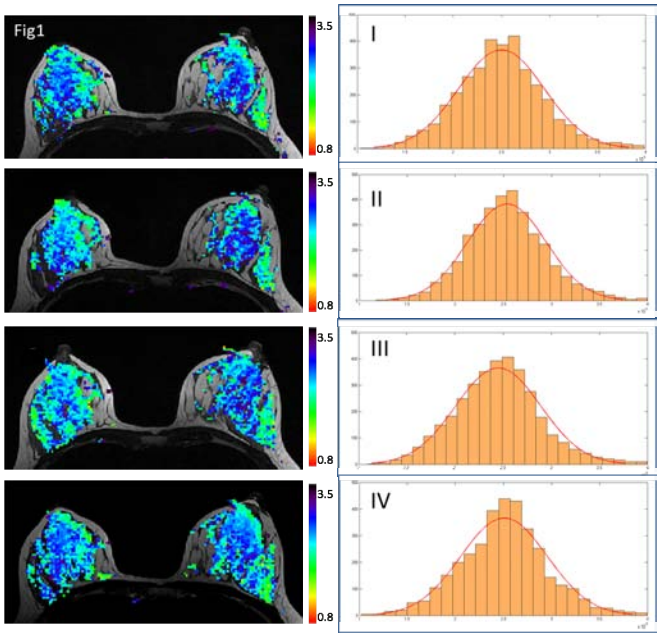

Fig. 1. **Parametric maps and the distribution histograms of λ1 of OCs-free 27 yo premenopausal woman during the menstrual cycle**. I-IV: week of the scan during the menstrual cycle. λ1 is in units of x10^{-3} mm^2/s.

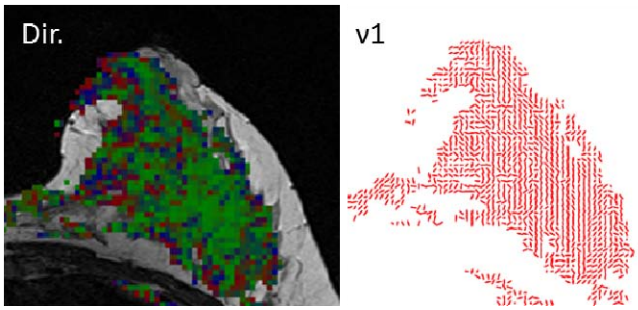

Fig. 2. Direction and vector maps of a lactating breast (age: 30). The direction map represents the direction of the 1st principal eigenvector in a three color code: red: lt <--> rt; green: head <--> feet; blue: ant <--> post. The vector map presents in white sticks the direction of the 1st principal eigenvector v1

In summary: DTI parameters are not sensitive to the menstrual cycle changes, while menopause, long term HRT and the presence of milk in lactating women affected the diffusion tensor parameters. Therefore, the timing for performing breast DTI is not restricted throughout the menstrual cycle, whereas the modulations in diffusion parameters due to HRT and lactation should be taken into account upon DTI evaluation.

References: 1. Kuhl C et al *Radiology* 2007;244(2):356-78. 2. Sardanelli F et al *EurJ Cancer* 2010;46(8):1296-316. 3. Partridge SC *J Magn Reson Imaging* 2010;31(2):339-47. 4.Partridge SC et al *Magn Reson Imaging* 2010;28(3):320-8. 5. Eyal E et al Proc. Intl. Soc. Mag. Reson. Med. 18, p362 2011. 6. Eyal E et al *Invest Radiol* 2012;47(5):284-91. 7. Baltzer PT et al *Eur Radiol* 2011;21(1):1-10. 8. Partridge SC et al *J Magn Reson Imaging* 2001;14(4):433-8. 9. O'Flynnet al EM *Eur Radiol* 2012;22(7):1512-8. 10.Clendenen TV et al *Magn Reson Imaging* 2013;31(1):1-9. The help of Dr T. Kushnir, Mr. N. Stern and Mrs. F. Attar is gratefully acknowledged. HD holds the Fred and Andrea Fallek Chair for Breast Cancer Research.