Abstract

Owing to technical advances and improvement of the software, diffusion weighted imaging and diffusion tensor imaging (DWI and DTI) greatly improved the diagnostic value of magnetic resonance imaging (MRI) of the pelvic region. These imaging sequences can exhibit important tissue contrast on the basis of random diffusion (Brownian motion) of water molecules in tissues. Quantitative measurements can be done with DWI and DTI by apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values respectively. ADC and FA values may be changed by various physiological and pathological conditions providing additional information to conventional MRI. The quantitative DWI assists significantly in the differentiation of benign and malignant lesions. It can demonstrate the microstructural architecture and cellular density of the normal and diseased uterine zones. On the other hand, DWI and DTI are useful for monitoring the treatment outcome of the uterine lesions. In this review, we discussed advantages of DWI and DTI of the normal and diseased uterus.

Key words: Magnetic resonance imaging; Diffusion weighted imaging; Diffusion tensor imaging; Uterus

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and monitoring the treatment outcome of the uterine diseases.

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INTRODUCTION

Diffusion weighted imaging (DWI) is a magnetic resonance imaging (MRI) sequence structured on the basis of diffusion (Brownian motion) of water molecules in the extracellular space and is being increasingly used to evaluate the female pelvis. The quantitative parameter acquired from DWI sequences is the apparent diffusion coefficient (ADC) value. The basic factors affecting the ADC values are tissue structures, interactions between the molecules and cellular density. Thus, ADC is altered by many physiological and pathological conditions of the body[6].

Uterus is a fibromuscular solid organ under the effect of the hormones and is composed of three layers: the endometrial, the junctional and the myometrial zones. Physiological (menstrual cycle, menopausal period) fluctuations of these zones change the ADC values used in the evaluation of uterine abnormalities[6].

Diffusion is a multi-dimensional process, which occurs in different values in different directions depending on the microstructure of the tissues. Since uterine myometrium is composed of smooth muscle bundles and connective tissue diffusion reflects anisotropic features. Though DWI gives information about the direction of diffusion and cellularity of the tissue, anisotropic characteristics of tissues can be assessed appropriately by diffusion tensor imaging (DTI). It can be used to detect water diffusion directionality which in turn shows the microstructural architecture of normal and diseased tissue. Fractional anisotropy (FA) is the main quantitative parameter obtained from DTI data. Initially DTI has been used to show and evaluate the integrity of white matter tracts in neuroradiology. With the improvement of the MRI hardware and softwares, fast imaging techniques, after the use of DWI also DTI was implemented to abdominal imaging for some of the abdominal organs like uterus. The initial researches have been published regarding DTI of the uterus specimens of the patients to whom hysterectomy was performed for medical reasons[6-8] and then in vivo on the uterus of the patients[9].

Non-functional (conventional) MRI provides excellent anatomical information of the uterus, however, the morphological appearance still may not differentiate some of the benign and malignant uterine lesions[8]. DWI and DTI which provide functional information and when combined with conventional MRI become a complementary diagnostic tool for the uterus and giving more information for the differentiation and extension of benign and malignant lesions, and for the follow up of treatment outcome after uterine arterial embolization (UAE), oncological therapies[7].

In this paper, we aimed to focus on and review their diagnostic importance of the DWI and DTI techniques of the normal and diseased uterus.

DWI AND DTI TECHNIQUE

Optimal MRI of the female pelvis should be performed on a high field strength MRI system (1.5 or 3 T) using local phased-array coils. High field strenght MRI and phased-array coils increase the signal-to-noise ratio, provide high resolution images for the DWI and DTI sequences. Besides development of ultra-fast pulse sequences such as echo-planar imaging and parallel imaging technique, enabled to prevent motion artefacts and consequently functional MRI of the female pelvis[8].

For conventional MRI T1, T2 and fat saturated T2-weighted fast spin echo sequences followed with pre and post contrast three dimensional gradient-recalled echo volumetric interpolated breath-hold sequences and three plane imaging is necessary which give morphological information about the uterine zones. The addition of DWI and DTI sequences to the conventional MRI gives functional data about the uterus.

DWI is acquired by the measurement of signal loss after a series of two motion-providing gradient (MPG) pulses with the addition of a 180° refocusing radio frequency pulse to both sides for enhancing the variations of molecular diffusion between tissues. The density of MPG pulses is shown by the $b$-value, an paramount criterion affecting the signal intensity of the DWI[7]. An appropriate $b$ value is necessary for the female pelvic MRI.

In several studies, DTI has been used to demonstrate fiber structures of the ex vivo uterus, because of problematic conditions leading to artefacts such as body motions, heartbeat, intestinal and respiratory movements, and uterine peristalsis[2-4]. Fiocchi et al[5], examined the DTI of in vivo uterus with a 3 T MRI using a 3D tractography algorithm and revealed that DTI is useful for imaging fibre architecture of in vivo human uterus.

DWI AND DTI OF NORMAL UTERUS

In reproductive age groups, T1 and T2 signal intensity characteristics of the uterine zones (endometrial, junctional and myometrial) demonstrate variations during ongoing phases of the menstrual cycle and with menapausal status. Physiological fluctuations affect the normal ADC values used in the evaluation of uterine pathologies[8].

On conventional MRI, the endometrial zone reflects high signal on T2-weighted sequences, however not so high like urinary bladder and low signal intensity on
The menstrual cycle includes three different phases. The initial four days of the menstrual phase is named as menstruation. On the fifth day the proliferative (follicular) phase begins and continues until the ovulation which is estimated to occur on the 14th day of the menstrual cycle. The secretory (luteal) phase begins with ovulation and lasts on the first day of the next menstrual period. Tsili et al[13], reported that the ADC values of the endometrial and myometrial zones were different in the three phases of the cycle (menstrual phase: 1.25 ± 0.27, 1.91 ± 0.35; proliferative phase: 1.39 ± 0.20, 1.72 ± 0.27; secretory phase: 1.50 ± 0.18, 1.87± 0.28, respectively). A wide variation of ADC values of normal endometrial and myometrial zones is detected during different periods of the menstrual cycle. These variations probably depends on the physiologic-histologic fluctuations[14]. In the menstrual period, periodic contractions of the spiral artery walls in the normal endometrial zone, cause interruption of the epithelium and rupture of the vessels. Endometrial discharge caused by the torn ends of venous structures, arteries and glands result in restricted diffusion in the endometrial zone during the menstrual phase. In the secretory phase, expanded uterine glands, prominent arteries in the normal endometrial zone, accompanied by less amount of cells in stratum basalis and higher interstitial fluid can be among the probable explanations for the higher ADC values[13].

Kido et al[15], examined both intraindividual and interindividual differences of the ADC values of the normal uterine zones during the phases of the menstrual cycle in young age group. In this report, the ADC values for myometrial and endometrial zones were lower in the menstrual phase in comparison to the periovulatory and the secretory phase, although significant variability among individuals was reported. These preliminary results must be kept in mind, that the menstrual cycle and individual differences in reproductive women should be taken into account during the interpretation of the ADC values of uterine zones[11].

Kuang et al[16], studied the ADCs of the normal uterine zones during different periods of the menstrual cycle between reproductive women with different ages. The ADC values of the uterine zones were statistically different from each other. Endometrial ADC values of the females in their 30 s were higher than the ones in their 20 s and in their 30 s in the midproliferative and midsecretory periods. Also the ADC values of endometrial zone for all age groups were lower in the midproliferative phase in comparison to midsecretory phase, however the ADC values of the myometrial and junctional zones were not statistically different between the phases and age groups. According to this study patient age, menstrual period and the zone evaluated should be taken into consideration during quantitative evaluation[16].

The relationship of the uterine zonal ADC values were investigated by Fornasa et al[17], between the different periods of the cycle. The ADC values of the endometrium calculated on the fifth day of the cycle were lower when compared with periovulatory ADC values at the fundus (mean 0.923 mm²/s vs 1.256 × 10⁻³ mm²/s) and at the isthmus (mean 1.297 mm²/s vs 1.529 × 10⁻³ mm²/s). Ischmic endometrial ADC values were higher than the fundal ADC values (mean 1.420 × 10⁻³ mm²/s vs 1.132 mm²/s). These findings were statistically significant. Physiological fluctuations occurring in the ADC values of the endometrium of normal females should be kept in mind during the interpretation of the DW images of the patients[15].

DTI revealed two basic systems of fibers: circular and longitudinally oriented fibers as shown ex-vivo. Examination of the non cesarean scarred uteri showed anisotropy and fiber directions could be depicted[5]. Knowledge of the architectural data can help to understand the details of functionality during gestation and birth. The connective tissue architecture in the uterus of reproductive age is composed of three different layers. The first inner layer is a non-organized cluster-like interweaving of the fiber complex, secondly circular fibers in the middle layer and finally longitudinal fibers in the exterior layer[16]. In the postmenopausal uterus, the cervical region primarily includes well oriented longitudinal fibers[4].

Fiocchi et al[5], argued that two third of the caesarean scarred uteri had altered fiber structure in comparison to normal uteri in sutural zone. Numeric data of 13 volunteers (8 nulliparous- I group, 5 with caesarean delivery- II group) revealed lowest regional fiber number and density in the anterior isthmic portion (respectively 105, 77 and 9.3, 6.7), suture localization, especially in two patients with a big scar caused placental complication at subsequent delivery. The mean FA and ADC of the whole uterus were 0.4 ± 0.0 and 3.4 ± 0.4 × 10⁻³ mm²/s respectively. The ADC of group I was higher than group II, but not statistically significant. In this study they concluded that 3 T DTI may show in-vivo human uterine fiber structures and may detect significant caesarean scars which may lead to subsequent placental...
metastatic lymph nodes with high signal against suppressed background signal of normal tissues, and this sequence may be used like a positron emission tomography image for fast and accurate cancer detection (Figure 1).

Myometrial lesions

The most frequent lesions encountered in the myometrial zone are fibroids. These are benign overgrowths of uterine muscle, reported to be probably to be found in up to 70% of females of reproductive age [22]. Myometrial malignant lesions are leiomyosarcomas and stromal sarcomas [23]. Some of the benign fibroids, in association with different types of degeneration or cellular types may lead to high signal intensity on T2-weighted sequences. Thus, the discrimination of benign and malignant myometrial lesions are challenging on conventional MRI.

Tamai et al [24] reported that DWI may be an useful for discriminating uterine sarcomas from benign fibroids. The ADC values of normal myometrial zone and degenerated fibroids were higher than uterine sarcomas and there was no overlap; however, there was an overlap with non-degenerated and cellular fibroids [24]. Pathological examination of the large fibroids with central necrosis revealed fibrosis. This finding was consistent with isotropic diffusion in DTI of the associated lesion. Fibrotic leiomyomas include non-parallel collagen fibrils, whereas...
there were well-structured collagen bundles neighbouring to smooth muscle cells in the normal myometrial zone\[25,26\]. Irregularity of these collagen bundles could be the reason for the lower degree of anisotropy in the fibroids when compared with the neighbouring myometrium.

The ADC values may also be beneficial for determining the therapeutic outcome after UAE, radiotherapy and/or chemotherapy\[7\]. The effect of UAE or focused ultrasound may be evaluated by the detection of ablated tissue with DWI. The ADC values of fibroids after treatment are lower when compared with initial ADC values\[27,28\].

**Endometrial lesions**

The most frequent gynecologic malignancy is endometrial cancer. It should be discriminated from benign hyperplasia of the endometrium along with polyps. The ADC value of polyps (1.27-1.58 × 10⁻³ mm²/s) and of normal endometrial zone (1.53 × 10⁻³ mm²/s) is significantly higher than endometrial cancer (0.88-0.98 × 10⁻³ mm²/s)\[24-29\] (Figures 2 and 3).

Histologic grade, stage, level of myometrium invasion, existence of nodal metastases, invasion of lymphoid and vascular structures all effect the prognosis of endometrial cancer. However the most important factor effecting prognosis is the depth of myometrium invasion\[30\]. The success of DWI has been improved in the assessment of accurate myometrium invasion detection and in differentiating tumor recurrence from post-therapeutic findings\[31\]. The first surgical staging of endometrial cancer was proposed in 1988, and than the update of the International Federation of Gynecology and Obstetrics (FIGO) staging was done in 2009\[32\]. In this revised FIGO staging system, stage I A tumors include the tumors invading solely the inner half of the myometrial zone and the tumors confined to endometrium\[32,33\]. Tumors infiltrating the exterior half of the myometrial zone are defined as stage I B tumors. These revisions include simplification of stage I disease and determination of cervical infiltration as a distinct stage to increase the diagnostic value of MRI\[30\].

According to Fuji et al\[29\], the ADC value was 84.6% successful in detecting endometrial cancer. Toba et al\[2\] investigated the feasibility of DTI for evaluating the myometrial invasion of endometrial cancer. The degree of myometrium invasion was subgrouped as stage E (confined to endometrial zone), more than 50%. The ADC values of the cancer, inner or exterior myometrial zones were not statistically different. Tumoral FA values (0.21 ± 0.05) were lower than the inner layer of the myometrial zone (0.44 ± 0.01) and exterior myometrium (0.32 ± 0.08) (P < 0.01). The inner or exterior myometrial FA values, (0.45 ± 0.05 vs 0.43 ± 0.04) were not statistically different in stage E cancers. However, in stage S and D tumors the FA values of the inner or exterior myometrial FA zones were significantly different (0.5 ± 0.05 vs 0.3 ± 0.04, P < 0.01; 0.39 ± 0.03
vs 0.22 ± 0.01, $P < 0.01$; respectively). Myometrial infiltration of endometrial tumor may be detected with the disruption of the anisotropic layer.

DWI and DTI have a potential role for the discrimination of benign and malignant endometrial masses. It may also give additional information for preoperative assessment and should be performed as a part of routine MRI for endometrial tumors. Besides, DWI is a useful technique increasing the accuracy of staging\cite{30}.

**Cervical lesions**

Cervical cancer is a common gynaecological tumor. However, its incidence has decreased in developed countries as a result of screening with the Papanicolaou test (Pap smear), cervical cancer is still an important cause of tumor-related death in developing countries\cite{34}.

ADC measurements made significant supplement for the discrimination of normal cervical zone and cancers preoperatively. Besides there was correlation between tumor type, stage and ADC values\cite{35}.

According to McVeigh et al\cite{36} the average median ADC of normal cervix was statistically higher than cervical cancers ($2.09 \times 10^{-3} \text{ mm}^2/\text{s}$ vs $1.09 \times 10^{-3} \text{ mm}^2/\text{s}$), and returned to the normal level following

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**Figure 3** A 42-year-old woman with endometrial polyp. A: Hypointense polyp in the endometrial cavity on sagittal T2-weighted image mimicking low grade endometrial carcinoma (arrows); B: Sagittal contrast-enhanced T1-weighted image with fat suppression shows enhancing endometrial polyp (arrows); C: On the axial DWI ($b = 1000 \text{ s/mm}^2$) image, the mass is hypointense clearly excluding malignancy (arrows); D: Corresponding axial apparent diffusion coefficient (ADC) map. The ADC value within the mass is $1.85 \times 10^{-3} \text{ mm}^2/\text{s}$.

**Figure 4** Thirty two years old volunteer. A: Sagittal T2-weighted image of a normal uterus; B: 3D whole tractography image of the normal uterus. Red colors represent a right-left orientation, blue represents a crano-caudal orientation and green represents an antero-posterior orientation of diffusion. Changes in the intensity of the color represent different strengths of anisotropy.
CONCLUSION

According to this review, DWI and DTI emerge to be applicable and reliable sequences for the determination of physiological fluctuations of the uterus, detection of malignant lesions of the uterus and monitoring the therapeutic outcome. When combined with conventional MRI sequences, DWI and DTI provide further data about physiological and pathological conditions of the uterus. DWI and DTI are noninvasive, do not cause radiation exposure or need for contrast injection.

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