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Relationship between Magnetic Resonance Relaxometry R2 Value and Iron Levels and the Severity of Dysmenorrhea in Patients with Ovarian Endometrioma

Hiroshi Kobayashi[1,2]* and Shogo Imanaka[1,2]

[1]Department of Obstetrics and Gynecology, Nara Medical University, Kashihara, Japan
[2]Department of Infertility and Gynecology, Ms.Clinic MayOne, Kashihara, Japan

Abstract

Objective: Magnetic resonance (MR) relaxometry is a diagnostic imaging method that enables non-invasive quantification of iron levels in patients with endometriosis. The aim of this study is to investigate whether cyst fluid (CF) MR relaxometry R2 values are associated with iron levels and the severity of dysmenorrhea in women with ovarian endometrioma (OMA).

Methods: A single-center prospective cohort study was conducted by collecting data from patients admitted to the Department of Gynecology, Nara Medical University Hospital, Kashihara, Japan, from February 2013 to July 2019. Fifty patients aged 21-54 years who were histologically diagnosed with OMA were enrolled. CF R2 values were measured preoperatively using MR relaxometry. The severity of dysmenorrhea was classified into four groups based on the Numeric Rating Scale (NRS-11): painless, mild, moderate, and severe. The association between clinicopathological features and CF iron levels and R2 values was analyzed.

Results: The mean (± SD) age of women was 36.58 ± 7.16 years. The mean CF R2 value was 23.83 ± 10.16 s-1. There were no significant differences among the four groups in variables regarding age at diagnosis, parity, preoperative serum CA125 and CA19-9 levels, tumor diameter, and tumor localization (unilateral or bilateral). CF iron levels were significantly correlated with the severity of dysmenorrhea (P=0.001). A significant positive correlation between preoperative CF R2 value and iron level was detected (r = 0.608, P=0.001). However, there was no significant correlation between R2 values and the severity of dysmenorrhea.

Conclusion: R2 values showed a significant positive correlation with iron levels, but were not associated with the severity of dysmenorrhea.

Keywords: Endometriosis; Dysmenorrhea; Magnetic Resonance Relaxometry; R2 Value

Correspondence to: Hiroshi Kobayashi, Department of Obstetrics and Gynecology, Nara Medical University, Kashihara, Japan; Tel: +81-744-29-8877; Fax: +81-744-23-6557; E-mail: hirokoba@naramed-u.ac.jp

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Introduction

Endometriosis is one of the most common gynecologic diseases that affects around 5% of reproductive age women [1]. The disease is characterized by estrogen-dependent growth characterized by the presence of endometrial tissue outside the uterus [1]. Endometriosis causes dysmenorrhea, infertility, and an elevated risk of epithelial ovarian cancer (endometriosis-associated ovarian cancer, EAOC) and is significantly associated with worse quality of life [2]. We have previously reported that iron in endometriotic cysts is closely associated with endometriosis-related symptoms [3-5]. First, there was a positive correlation between the presence and severity of dysmenorrhea and cyst fluid (CF) iron levels (P <0.001) [5]. Second, CF iron levels were significantly higher in infertile women compared to non-infertile women (P=0.019), and was an independent predictor of OMA patients complaining of infertility [4]. Finally, patients with EAOC had significantly lower iron levels than benign endometriotic cyst sample (P<0.001), indicating that iron can be the preferred biomarker in clinical practice for the diagnosis of EAOC in OMA patients [3]. The practical clinical and biological significance of iron is still unknown, but several hypotheses have been proposed [2,6]. Iron in endometriotic cysts causes oxidative stress damage and can induce redox stress. OMA is characterized by intracystic bleeding, in which hemoglobin is released from red blood cells. Hemoglobin in the cyst is converted to methemoglobin during autoxidation and releases superoxide anions [6]. On the other hand, free iron released from hemoglobin produces hydroxyl radical through the Fenton reaction [6]. It has been demonstrated that reactive oxygen species (ROS) such as superoxide and hydroxyl radical play a pivotal role in inflammatory pain and neuropathic pain mechanisms [7,8]. Endometriotic lesions with adhesions and deep infiltration in the pelvic organs cause disease-related pain. Some papers reported that OMA itself is associated with pain symptoms [9], while other papers reported that none of the specific features of OMA, including lesion size, are associated with the severity of dysmenorrhea [10]. In addition to pathological abnormalities such as adhesions, humoral factors such as ROS can also cause dysmenorrhea. Oxidative stress also causes damage to sperm and oocytes and is associated with unexplained infertility [11,12]. Furthermore, there is some evidence that oxidative stress is associated with malignant transformation of endometriosis [13].

Since the iron measurements are limited by the need for invasive surgery, a non-invasive quantification method is desired. The iron distribution in the brain, liver and heart using MRI is provided by measuring the effective transverse relaxation rate [14,15]. In 2017, Yoshimoto et al. succeeded in non-invasive measurement of iron level in CF of OMA and ovarian cancer using MR relaxometry R2 value [16]. The MR relaxometry-based parameter R2 value showed a significant positive correlation with the iron levels [16]. Currently, MR relaxometry is the imaging modality that enables quantitative diagnosis of iron levels in ovarian tumors [16-18]. If iron levels correlate with the presence and severity of subjectively determined dysmenorrhea and iron levels correlate with R2 values, then R2 values may be associated with the severity of dysmenorrhea. Here, we investigate whether preoperative R2 values are associated with the presence and severity of dysmenorrhea subjectively determined by OMA patients. We are not asking an expensive radiologic study to discover a parameter that would validate or discredit a patient's subjective report of dysmenorrhea. This study is a proof-of-concept for a non-invasive model for MR relaxometry via iron level quantification.

Methods

Patient Selection and Analytic Cohort

The study was conducted under the guidelines that had been approved by the medical ethics committee of the Nara Medical University (2012-951). Written informed consent was obtained from each patient. A single-center prospective cohort study was conducted by collecting data from patients admitted to the Department of Gynecology, Nara Medical University Hospital, Kashihara, Japan, from February 2013 to July 2019. Participants underwent surgery or active surveillance for endometriosis management. The following inclusion criteria were used:

1. Cases undergoing surgery with removal of lesions for histological evaluation;
2. Patients with pathological confirmation of endometriosis;
3. Patients coexisting with OMA; and
4. Patients whose parameter R2 value (s^{-1}) was measured preoperatively.

All patients with endometriosis who participated in this study underwent excisional surgery for ovarian endometrioma. Patients without OMA are not included in this study. In principle, laparoscopic surgery was used to treat patients with endometriosis. Cyst fluid is collected during surgery in all patients. All visible cyst fluids were aspirated during laparoscopic surgery from OMA. The aspirated cyst fluid was collected and stored as a sample. The rASRM scoring system was used to evaluate the severity of endometriosis. The criteria for exclusion were:

1. Age below 20 years;
2. Women during menstruation (increased iron concentration due to intracystic bleeding);
3. Postmenopausal women;
4. Women coexisting with adenomyosis;
5. Patients with malignant transformation;
6. Women who received hormone treatment within 3 months.

All participants were recommended to undergo magnetic resonance imaging (MRI) after routine transvaginal ultrasonography (TVS) for preoperative evaluation of endometriosis. TVS was performed by experienced operators with a special interest in endometriosis with a single ultrasound system (Voluson E8; GE Healthcare, Tokyo, Japan) using a transvaginal transducer (5-7.5 MHz). MRI was obtained on a 3T system using T1W and T2W sequences (Magnetom Verio, Siemens Healthcare, Erlangen, Germany). Following MRI examination, the registered patients underwent MR relaxometry by using single-voxel acquisition mode sequence at a multiple echo times and by fitting an exponential decay to the echo amplitude at different multiple echo times as described [16]. A parameter R2 value (s^{-1}) was calculated using high-speed $T^{*}2$ -corrected multi-echo MR sequence (HISTO) by the 3T-MR system [16]. Imaging diagnosis, including TVS, MRI and MR relaxometry, was completed within 4 weeks prior to surgery. Medical records were comprehensively reviewed, and variables such as patient's age at diagnosis, parity number, symptoms (the severity of dysmenorrhea), menopausal status, preoperative serum CA125 levels, preoperative serum CA19-9 levels, surgery date, maximal tumor diameter, laterality of tumor were collected.

Definition of Pelvic Pain

The Numeric Rating Scale (NRS-11) is one of several pain scales that are used clinically to evaluate the severity of dysmenorrhea [19,20]. Using the 11-point NRS, 0 point was classified as "painless", 1-3 points as "mild pain" (no use of analgesics), 4-6 points as "moderate pain" (analgesics used but generally improved) and 7-10 points as "severe pain" (pain does not improve even if analgesics are used, which strongly interferes with daily activities).

Statistical Analysis

SPSS 25.0 (IBM Japan) statistical software was used for the statistical analysis. The data were presented as mean and standard deviation (SD) or median and range. Data distribution was verified by the Shapiro-Wilk test. Comparison of categorical variables between groups was performed using the Tukey's HDG and Chi-square test. The Kruskal-Wallis test was used to compare CA125, CA19-9, tumor diameter, iron level, and R2 value among the four groups. The correlations between two parameters were analyzed using Pearson correlation and linear regression models. Validation of the expression levels of R2 value was performed using a box plot to visualize the difference in its expression based on the severity of dysmenorrhea. Differences with $P < 0.05$ were considered statistically significant.

Results

Two hundred and thirty nine patients were enrolled in the study. Figure 1 illustrates the detailed selection process for study design. All patients collected cyst fluid during surgery and measured iron levels. Laparoscopic surgery for patients with endometriosis was scheduled primarily on Mondays and Fridays. Patients were hospitalized the day before surgery, but patients who underwent surgery on Monday were unable to undergo MR relaxometry on Sunday. Finally, eighty-seven women measured preoperative R2 values using MR relaxometry. Of the 87, 37 were excluded based on specific exclusion criteria. Eventually, a total of 50 patients were included in this study. Six patients were rASRM stage 1 (12%), 10 were stage 2 (20%), 16 were stage 3 (32%), and 15 were stage 4 (30%). The rASRM stage was unavailable in 3 cases (6%).

Patient demographic and clinicopathological characteristics of the study population are summarized in Table 1. The mean age of participants was 36.58 ± 7.16 (ranged, 21-53 years). There were no significant differences among the four groups classified by the severity of dysmenorrhea in variables regarding age at diagnosis, parity, preoperative serum CA125 and CA19-9 levels, tumor size and tumor localization (unilateral or bilateral). There was a statistically significant positive correlation between CF iron levels and the severity of dysmenorrhea (P = 0.001). The average CF R2 level in all cases was 23.83 ± 10.16 s^{-1} (range, 6.73-48.65 s^{-1}). The difference in CF R2 values was not significant among the four groups (P = 0.239). Furthermore, the four groups were classified into 'No pain' vs. 'Mild + Moderate + Severe', 'No pain + Mild' vs. 'Moderate + Severe' and 'No pain + Mild + Moderate' vs. 'Severe', but there was no significant difference in CF R2 values as shown in Figure 2. We finally investigated the correlation between the CF iron levels and R2 values. As depicted in Figure 3, a significant positive correlation between R2 value and iron level was detected (r = 0.608, P=0.001).

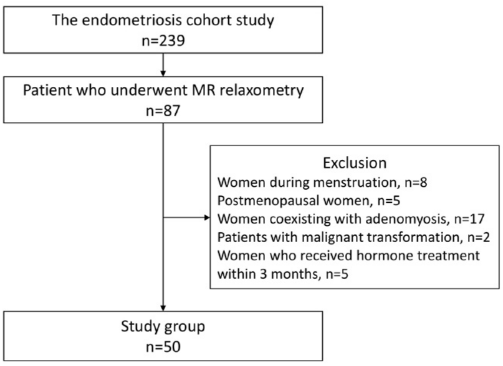

Figure 1: Flow diagram of patient selection and exclusion.

The left shows the CF R2 values in the 2 groups, "No pain" and "Mild pain + Moderate pain + Severe pain". The center shows the CF R2 values in the 2 groups, "No pain + Mild pain" and "Moderate pain + Severe pain". The right shows the CF R2 values in the 2 groups, "No pain + Mild pain + Moderate pain" and "Severe pain".

R2 value was significantly correlated with iron level (Y= 0.042X + 13.805; P=0.001, r = 0.608). The X-axis and Y-axis show the CF iron level and R2 value, respectively.

Discussion

In this study, we compared the degree of dysmenorrhea and both iron level and R2 value. The degree of dysmenorrhea was positively associated with iron level, and a positive correlation was found between two of the individual measurement, namely, iron level and R2 value. However, the R2 value was not correlated with the severity of dysmenorrhea. R2 value is considered inferior to iron level to assess the severity of dysmenorrhea as, in some cases, R2 value overestimates iron level (Figure 3).

First, quantitative mapping of MR relaxation rate (R2 value) is a non-invasive method for measuring iron concentration. Yoshimoto et al. tested the relaxometry protocol in a phantom study and then applied it to a real clinical case study, including a variety of benign and malignant ovarian tumors [16]. CF R2 values were highly correlated with iron levels, frequently elevated in patients with endometriosis, but extremely down-regulated in patients with ovarian cancer. Currently,

Table 1: Demographic and clinical characteristics of four groups classified by the severity of dysmenorrhea.

		No pain (n=8)	Mild (n=16)	Moderate (n=18)	Severe (n=8)	*p*-value
Age	Mean ± SD	39.5 ± 7.6	35.3 ± 7.6	36.4 ± 7.3	36.6 ± 6.0	0.441[1]
Parity	0	2	9	10	5	0.478[2]
	≥1	6	7	8	3	
CA125	Median (range)	77.5 (11.0-302.0)	51.5 (16.0-235.0)	59.5 (22.0-1504.0)	102.0 (22.0-194.0)	0.396[3]
CA19-9	Median (range)	18.5 (11.0-30.0)	30.5 (10.0-392.0)	25.0 (1.0-39.0)	35.0 (15.0-55.0)	0.636[3]
Tumor diameter	Median (range)	66.0 (34.0-110.0)	72.0 (30.0-136.0)	68.0 (36.0-193.0)	54.5 (40.0-112.0)	0.685[3]
Localization	Unilateral	7	11	13	3	0.222[2]
	Bilateral	1	5	5	5	
CF iron level	Median (range)	124.9 (72.8-289.3)	224.7 (65.3-695.7)	337.3 (71.3-477.3)	448.7 (315.2-1046.3)	0.001[3]
CF R2 value	Median (range)	24.4 (20.7-47.8)	18.1 (7.0-43.0)	23.1 (6.7-48.7)	22.6 (13.1-40.5)	0.239[3]

[1]Tukey HSD; [2]chi-square test; [3]Kruskal Wallis test; CA125, Carbohydrate antigen 125; and CA19-9, Carbohydrate antigen 19-9; CF, cyst fluid.

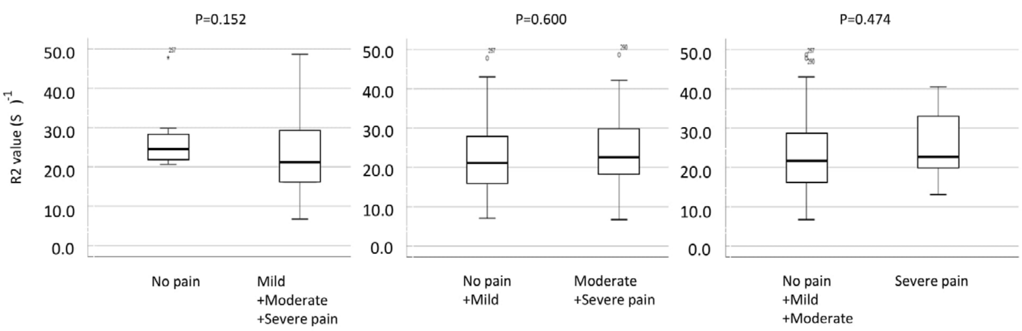

Figure 2: Validation of differential expression of R2 values based on the severity of dysmenorrhea.

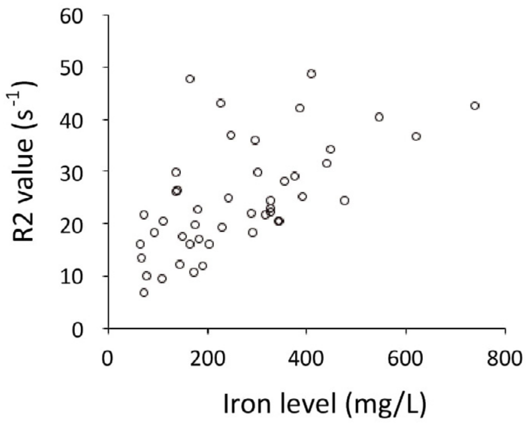

Figure 3: Scatter diagram for the correlation of R2 value with CF iron level.

preoperative R2 levels made it possible to distinguish benign or malignant in OMA patients with mural nodules, but the roles and possible clinical applications of iron are still under study [16-18]. Furthermore, recent research has demonstrated a positive correlation between the severity of dysmenorrhea and surgically collected CF iron levels [5]. In this study as well, we confirmed that iron levels were significantly correlated with the severity of dysmenorrhea (P=0.001). However, R2 value did not correlate with the severity of dysmenorrhea, suggesting that R2 value is inferior to iron level.

Second, why is the R2 value not associated with the severity of dysmenorrhea when the R2 value is positively correlated with iron levels and the iron level is correlated with the severity of dysmenorrhea? The median (± SD) iron levels for OMA and EAOC were 244.4 ± 204.9 mg/L and 14.2 ± 36.6 mg/L, respectively [3], indicating that there was a 17-fold difference in iron levels between the two groups. However, the difference in iron levels between the severe pain group and the no pain group was about four-fold (448.7 mg/L vs. 124.9 mg/L). The R2 value may not recognize the subtle differences in iron concentration. Furthermore, looking at the correlation diagram between the R2 value and the iron level, the R2 value is often higher than the expected iron level (the case in the upper left of the figure 3). This may be the reason why the R2 value does not correlate with the degree of pain. In the upper left case of Figure 3, the R2 values may recognize substances other than iron in the cyst contents. To date, it is not known exactly what metal ions other than iron are recognized by MR relaxometry. Research is being conducted on substances that affect R2 value. Non-invasive quantification that can measure only iron concentration is strongly desired to evaluate the severity of dysmenorrhea.

Third, to date, little is known about the markers associated with the severity of dysmenorrhea. There was a significant correlation between preoperative serum CA 125 levels and the endometriosis stage, lesion size, and adhesion score [21], demonstrating that CA 125 levels can be evaluated as a marker of disease spread and severity. However, some researchers have found no association between serum CA 125 levels and patient's complaints such as dysmenorrhea [10,22]. This means that the extent of the lesion does not correlate with the severity of dysmenorrhea. In addition, to assess endometriosis-associated pain, the sacral nerve root features were evaluated by the means of MRI-diffusion tensor imaging (DTI) tractography [23]. Pathological DTI findings correlate with the disease severity of endometriosis, namely the presence of deep infiltrating endometriosis (DIE) and strong adhesions, and also the severity of dysmenorrhea [23]. Evaluation of nerve fiber pathways with MRI-DTI tractography may help to better understand the severity of pain. However, this methodology has not been fully investigated in endometriosis.

Finally, the patients enrolled in this study include a certain number of OMA patients coexisting with DIE. Since deep infiltration, adhesions, and structural abnormalities due to endometriosis cause pain, it may be difficult to determine the severity of pain based solely on CF R2 levels. However, in this study, there was no difference in the rate of coexistence of DIE in the four groups (3 [37.5%], 7 [46.1%], 8 [44.4%], and 4 [50.0%] patients in the no pain group, mild group, moderate group, and severe group, respectively). At this time, iron level was superior to R2 value to assess the severity of pain. More patients may be needed to investigate whether R2 level helps assess pain severity. The pain assessment scales are subjective and easily influenced by individuals' emotional experiences [24]. Even if the R2 value correlates with the degree of dysmenorrhea, it should not be measured clinically to confirm pain.

Iron induces reactive oxygen species (ROS) production, promotes oxidative stress and inflammation, and damages not only DNA but also proteins and lipids, resulting in cell dysfunction [13]. Oxidative stress-induced inflammation in turn could mediate chronic diseases including not only endometriosis but also diabetes, cardiovascular disease, neurological diseases, and cancer [13]. There is an unmet need to develop an accurate non-invasive method for measuring iron or iron-induced ROS in clinical practice.

In conclusion, R2 value showed a significant positive correlation with iron level, but was not associated with the severity of dysmenorrhea. There is some discrepancy between R2 and iron measurements, which warrants further investigation and needs cautious interpretation.

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Statement of Ethics

The study was conducted under the guidelines that had been approved by the medical ethics committee of the Nara Medical University.

Patient Consent for Publication

Written informed consent was obtained from each patient.

Disclosure Statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Author Contributions

Hiroshi Kobayashi and Shogo Imanaka collected missing clinical and demographic information and laboratory data by electronic medical record review. Hiroshi Kobayashi made substantial contribution to conception of the study. Shogo Imanaka performed statistical work. The final version of the manuscript has been read and approved by all authors.

Availability of Data and Material

The datasets generated during the current study are available from Hiroshi Kobayashi on reasonable request.

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