

Original Article

Correlation Between Vertebral Marrow Fat Fraction Measured Using Dixon Quantitative Chemical Shift MRI and BMD Value on Dual-energy X-ray Absorptiometry

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Purpose : The purpose of this study was to determine whether there is a significant correlation between vertebral marrow fat fraction measured using Dixon quantitative chemical shift MRI (QCSI) and BMD on dual-energy X-ray absorptiometry (DXA).

Materials and Methods: This retrospective study included 68 healthy individuals [mean age, 50.7 years; range, 25–76; male/female (M/F) = 36/32] who underwent DXA of the L-spine and whole body MRI including QCSI of the L-spine and chemical shift MRI of the liver. The enrolled individuals were divided into subgroups according to sex and T-score [i.e., normal bone density (M/F=27/23) and osteopenia (M/F=9/9)]. Vertebral marrow (Dixon QCSI, TR/TE 10.2/4.8 ms) and hepatic fat fractions (chemical shift technique, TR/TE 110/4.9 and 2.2 ms) were calculated on MRI. We evaluated whether there were significant differences in age, body mass index (BMI), vertebral marrow fat fraction, or hepatic fat fraction among the subgroups. Whether or not the participant had reached menopause was also evaluated in females. The correlations among variables (i.e., age, BMI, vertebral marrow and hepatic fat fractions, BMD) were evaluated using Spearman's correlation method.

Results: There were no significant differences in age, BMI, or vertebral marrow and hepatic fat fractions between the two male subgroups (normal bone density vs. osteopenia). In female subjects, mean age in the osteopenic subgroup was greater than that in the normal subgroup ($p=0.01$). Presence of menopause was more common in the osteopenic subgroup [77.8% (7/9)] than the normal subgroup [26.1% (6/23), $p<0.05$]. The other variables showed no significant difference between female subgroups. The only significant correlation with marrow fat fraction after partial correlation analysis was that with age in the female subjects ($r=0.43$, $p<0.05$).

Conclusion: The vertebral marrow fat fraction calculated using the Dixon QCSI does not precisely reflect the mild decrease in BMD for either sex.

Index words : Bone mineral density · Bone marrow fat fraction · Hepatic fat fraction, aging
Magnetic resonance imaging (MRI)

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INTRODUCTION

Osteoporosis is the most common metabolic bone disorder, affecting 40% of women and 20% of men older than 50 years (1). Osteoporosis is characterized by reduced bone mass and disruption of bony microstructural integrity, leading to increased fracture susceptibility (2). Therefore, early detection and appropriate intervention for osteopenia and

osteoporosis are crucial to prevent potentially life-threatening osteoporotic vertebral or femur fractures.

Dual-energy X-ray absorptiometry (DXA) is a generally accepted diagnostic method for osteoporosis. Quantitative computed tomography (qCT) is an alternative with excellent spatial resolution. However, qCT is not used as a screening tool for osteoporosis due to the substantial radiation exposure (1, 2). Several previous studies have indicated that magnetic resonance imaging (MRI) has the potential for diagnosis of osteoporosis (1-5). The absence of radiation exposure is an advantage of MRI. MR spectroscopy has been used to detect decreased bone density or strength through the determination of vertebral marrow fat content (1, 3). However, MR spectroscopy is time-consuming and requires a skilled operator for precise data analysis (6). In addition, MR spectroscopy often reflects the marrow fat content in a small proportion of one lumbar vertebral body, whereas DXA BMD represents the average from the first to the fourth lumbar vertebral bodies.

To our knowledge, there has been only one study in the English literature on detection of osteoporosis using the chemical shift MRI technique. The study reported that there was no significant difference in vertebral marrow fat content calculated using chemical shift MRI among groups with normal bone density, osteopenia, or osteoporosis. However, most of the enrolled patients in the study were post-menopausal women, lacking information about males and other age groups. In addition, vertebral marrow fat content was only measured on the third lumbar vertebral body (7). Therefore, the purpose of the present study was to determine whether there is a significant correlation between the average marrow fat fraction of multiple lumbar vertebral bodies measured using Dixon quantitative chemical shift MRI (QCSI) and lumbar BMD.

MATERIALS AND METHODS

Patients

Seventy consecutive healthy individuals (mean age, 50.7 years; range, 25-76; male/female (M/F) = 36/34; pre-menopause/post-menopause = 20/14) who underwent DXA and whole body MRI for screening between October 2009 and January 2011 were included in this retrospective study. Two of the

enrolled subjects (one subject with severe degenerative change throughout the entire lumbar spine and one subject with multiple hemangiomas from the second to the fourth lumbar spines) were excluded because of the technical difficulties in appropriately placing the region of interest (ROI). As a result, 68 individuals were enrolled in this study. A radiologist who was blinded to the results of MRI retrospectively reviewed the medical records including BMD. None of the enrolled patients had a history of hematologic disorder, physical inactivity, malignancy, alcoholism, or chronic liver disease. Body mass index (BMI, kg/m²) was calculated in all enrolled subjects.

The male and female subjects were divided into two subgroups (normal bone density vs. osteopenia) according to T-score. Our institutional review board approved this study, and informed consent was waived.

Radiologic studies

DXA examination (Lunar Prodigy Advance, GE Healthcare, USA) of the lumbar spine from L1 to L4 and of the femur was performed in all enrolled subjects with a postero-anterior projection. Based on the 1994 World Health Organization (WHO) criteria, the T-score was calculated using the bone mineral density (BMD) value (g/cm²) in each subject as follows: (Patient's BMD) - (Mean Young-Adult BMD)/(1 SD of Young-Adult BMD) (8). According to the WHO criteria, osteoporosis, osteopenia, and normal bone density were defined as T-scores less than -2.5, between -1.0 to -2.5, and greater than -1.0, respectively (8, 9).

Whole body 1.5 Tesla-MRI (Magnetom Avanto, Siemens, Erlangen, Germany) was performed for screening in all enrolled subjects. Two radiologist (ten and eleven years of experience in body MR imaging) who were blinded to the clinical information and BMD retrospectively analyzed the MR images. T2 weighted sagittal images (TR/TE, 3300/100 ms; flip angle, 150°; section thickness, 4 mm; matrix, 448 × 403; number of excitation, 2.0; field of view, 450 × 450 mm²) were used to identify the variable pathological entities in lumbar vertebral bodies including degenerative change, anterior wedging, compression fracture, large Schmorl's node, intraosseous lipoma, hemangioma, hematologic disorder, or malignancy. Anterior wedging of the vertebral body was considered to be

present if the anterior to posterior height ratio of the vertebral body was less than 0.8. The marrow fat fraction was calculated using two-point Dixon techniques (TR/double TE, 10.2/4.8 and 7.1 ms; flip angle, 10°; section thickness, 4 mm; matrix, 384 × 288; NEX, 3.0; field of view, 280 × 280 mm²). In chemical shift MRI, the signals from water and fat are added in “in-phase” images (IP) and are subtracted in “opposed-phase” images (OP). Dixon QCSI relies on the phase shifts created by fat-water resonance frequency differences to separate water from fat and also provides “fat-only” and “water only” images (10). Gradient echo chemical shift in-phase and out-of-phase MRI (TR/double TE, 110/4.9 and 2.2 ms; flip angle, 70°; section thickness, 6 mm; field of view, 370 × 270; matrix, 256 × 134; NEX, 1.0) was used to quantify the hepatic fat fraction (11), which was measured to determine whether there was a significant correlation between the hepatic and vertebral marrow fat fractions.

Measurement of the vertebral marrow and hepatic fat fractions

Measurement of the vertebral marrow fat fraction was obtained on a PACS monitor (Picture Archiving and Communication System, PACS; Maroview, Marotech, Seoul, Korea) by two radiologists. Identical polygonal regions of interest (ROI) that were as large as possible were placed on each of the first to fourth lumbar vertebral bodies on the mid-sagittal water-only and fat-only images using the copy and paste function on the PACS monitor. The ROIs were located at least 3 mm from the endplate and the margin of each lumbar vertebral body to exclude peripheral pathological changes such as degenerative change. In addition, the lumbar vertebral portion demonstrating partial volume averaging and basi-vertebral veins was also excluded from the ROI (Fig. 1). The fat fraction of bone marrow on each lumbar vertebral body was calculated as “ $M_f / (M_f + M_w)$,” where M_f and M_w are the signal intensities of the fat-only and water-only images, respectively, as previously defined (12). The mean fat fraction of bone marrow from the first to

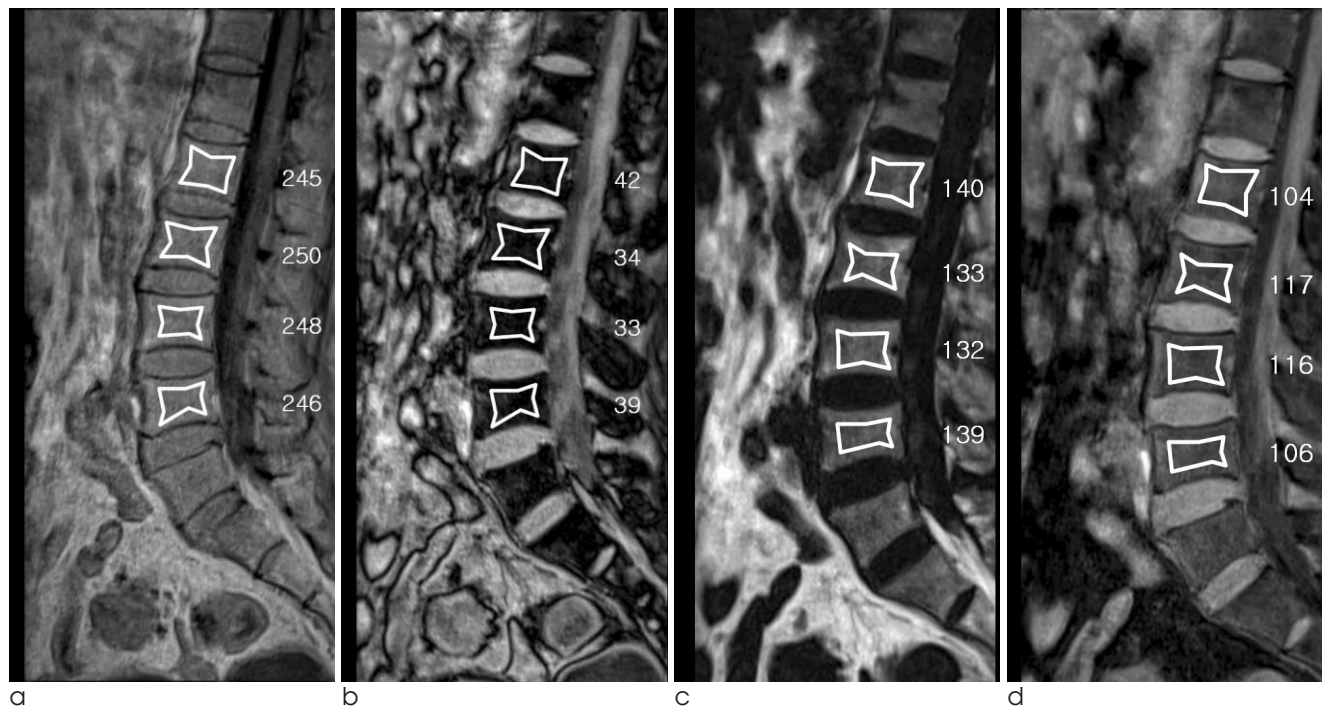


Fig. 1. Dixon QCSI calculated on the lumbar spine of a 75-year-old woman.

a-d. Indicate gradient echo T1 weighted sagittal in-phase, opposed-phase, water-only, and fat-only images, respectively. The polygonal “region of interest (ROI)” is placed in L1 to L4 bodies. Numbers indicate signal intensities in ROIs. On the (C) and (D) images, the fat fraction of the bone marrow is calculated using the equation $[M_f / (M_f + M_w)]$, where M_f and M_w indicate the signal intensities of the fat-only and water-only images, respectively. The calculated marrow fat fractions in the L1, L2, L3, and L4 regions were 0.42, 0.46, 0.47, and 0.43, respectively.

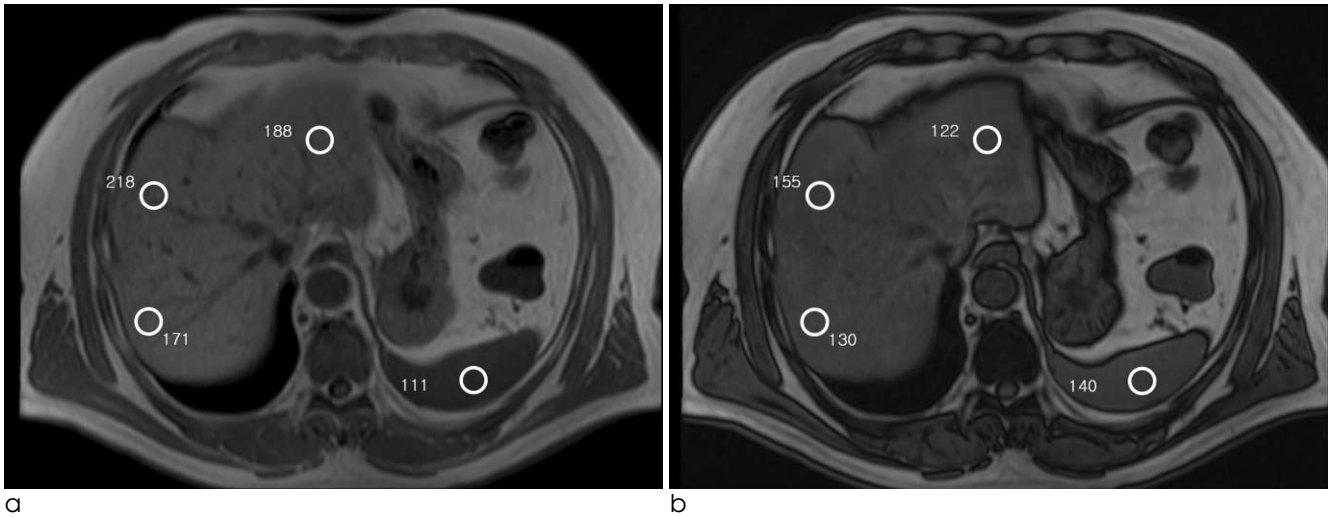


Fig. 2. Chemical shift MRI of the liver in-phase (A) and out-of-phase in a 52-year-old man.

Circular ROIs are placed in multiple locations to measure the hepatic fat fraction [one in the left lobe of the liver, two (anterior and posterior segments) in the right lobe of the liver, and one in the spleen]. Numbers indicate signal intensities in ROIs. Then, the hepatic fat-fraction is calculated using the equation $[(S_{IP} - S_{OP}) / 2 S_{IP}] * 100(\%)$, where S_{IP} and S_{OP} indicate the signal intensity in the liver divided by the signal intensity of the spleen on the IP and OP images, respectively. The calculated hepatic fat fraction was 22% in this patient.

fourth lumbar vertebral bodies was also calculated.

For quantification of the hepatic fat fraction, multiple circular ROIs larger than 105.3 mm^2 (200 pixel) were placed on the three hepatic areas lacking of artifact and vessel (the anterior and posterior segments of the right lobe and the left lobe at the level of bifurcation of the main portal vein) and on one splenic area in both IP and OP images (Fig. 2). The sizes and locations of the ROIs on both IP and OP were identical for each subject. Mean hepatic signal intensity on the IP and OP images was calculated as the sum of the three hepatic signal intensity divided by three. The hepatic fat fraction was calculated as “ $(S_{IP} - S_{OP}) / 2 S_{IP} * 100 (\%)$,” where S_{IP} and S_{OP} indicate mean hepatic signal intensity divided by splenic signal intensity on the IP and OP image, respectively (13).

Statistical analysis

All continuous variables were expressed as mean \pm SD. All statistical analyses were performed using Software Statistical Package for Social Sciences for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA). Inter-observer agreement of measured marrow fat fraction in each patient was calculated by using intraclass correlation. An averaged bone marrow fat fraction was used as a representative value. Age, BMI, BMD, vertebral marrow fat fraction and hepatic fat

fraction were compared between the subgroups using the Mann-Whitney U test. In the two female subgroups, menopausal status was compared using Fisher's exact test.

Bivariate Spearman's correlation coefficients were calculated among age, BMI, vertebral marrow and hepatic fat fractions, and BMD. A p value less than 0.05 was considered statistically significant. If there was a statistically significant correlation ($p < 0.05$) between two variables, a partial correlation coefficient was calculated while controlling the effects of other variables.

RESULTS

In five of 36 male subjects and three of 32 female subjects, one vertebral body was excluded from the measurement of bone marrow fat fraction in the MRI and BMD on the DXA due to the following causes: wedging ($n = 3$), vertebral fixation ($n = 1$), and non-visualization of the first lumbar vertebra ($n = 1$) in the male subjects; severe degenerative changes ($n = 2$) and blurring artifact ($n = 1$) in the female subjects. There was an excellent inter-observer agreement on the measurement of bone marrow fat fraction between two readers (intraclass correlation coefficient was

0.883). There were 27 subjects with normal bone density and nine subjects with osteopenia among the male subjects, and there were 23 subjects with normal bone density and nine subjects with osteopenia among the female subjects. The mean BMD of the male and female subjects were 1.2 .20.16 and 1.13 .10.18, respectively ($p > 0.05$). The mean vertebral marrow fat fractions in the male and female subjects were $0.52 \pm 0.08\%$ and $0.48 \pm 0.88\%$, respectively ($p > 0.05$). Age, BMI, BMD, vertebral marrow fat fraction and hepatic fat fraction in the male and female subgroups

are summarized in Table 1 and Table 2, respectively.

In the male subjects, there were no significant differences in age, BMI or vertebral marrow fat fraction between the two subgroups. In the female subjects, the mean age of the subgroup with osteopenia was greater than that of the subgroup with normal bone density ($p = 0.01$). Menopause was more common in the osteopenic subgroup [77.8% (7/9)] relative to the normal subgroup [26.1% (6/23), $p < 0.05$]. No other variables showed statistically significant differences between the female subgroups.

Table 1 Clinical and radiological data in the male subgroups

	Normal bone density group	Osteopenic Group	p value*
Included participants	27	9	
Age (years) +	52.6 ± 11.28	45.7 ± 10.19	0.19
BMI (kg/m ²) +	25.70 ± 3.38	24.95 ± 5.09	0.49
	25.5 ± 3.81		
BMD (g/cm ²) +	1.25 ± 0.15	1.04 ± 0.01	< 0.01
	1.2 ± 0.16		
Mean bone marrow Ff +	0.51 ± 0.08	0.54 ± 0.65	0.25
	0.52 ± 0.08		
Mean liver Ff (%) +	4.21 ± 8.48	0.78 ± 11.95	0.89
	3.55 ± 9.40		

Note.— + Data are presented as mean \pm SD

* Mann-Whitney U test between the two groups

BMI, body mass index; Ff, fat fraction

Table 2. Clinical and radiological data in the female subgroups

	Normal bone density	Osteopenia	p value*
Included participants	23	9	
Age (years) +	46.3 ± 6.96	57.1 ± 11.77	0.01
BMI (kg/m ²) +	23.18 ± 3.30	22.53 ± 3.97	0.65
	23.00 ± 3.45		
BMD (g/cm ²) +	1.23 ± 0.13	0.92 ± 0.07	< 0.01
	1.13 ± 0.18		
Mean bone marrow Ff +	0.47 ± 0.08	0.49 ± 0.11	0.71
	0.48 ± 0.88		
Mean liver Ff (%) +	2.87 ± 8.61	3.56 ± 14.99	0.97
	3.07 ± 10.52		

Note.— + Data are presented as mean \pm SD

* Mann-Whitney U test between the two groups

BMI, body mass index; Ff, fat fraction

In the female subjects, vertebral marrow fat fraction had a significant correlation with age and BMI ($r=0.49$ and $r=0.39$, $p < 0.05$). Age had a significant correlation with marrow fat fraction after the partial correlation analysis ($r=0.43$, $p < 0.05$), whereas BMI did not show a significant correlation with vertebral marrow fat fraction ($p = 0.51$). In the male subjects, there were no significant correlations between vertebral marrow fat fraction and the other variables. There were no significant correlations between mean BMD and the other variables for either sex.

Hepatic fat fraction had a significant correlation with BMI in both sexes ($r = 0.52$ and $r = 0.54$ in the male and female subjects, respectively, $p < 0.01$). However, the hepatic fat fraction did not show a significant correlation with mean BMD, vertebral marrow fat fraction, or age for either sex.

DISCUSSION

According to the WHO criteria, the diagnosis of osteoporosis is generally made by measuring BMD on DXA (8, 9). However, several previous studies have indicated the potential use of MRI in assessing bone marrow change for early detection or prediction of osteoporosis (14). Stem cells in the bone marrow differentiate into bone, cartilage or fat tissue under the effects of variable and complex regulatory factors including endocrine, paracrine and autocrine signals. As adipocytes and osteoblasts originate from the same marrow stem cells, an increase in the fat content of bone can be associated with a decrease in bone mineral density or bone strength (15). Previous studies have also indicated that an increase in the fat content of bone marrow was related to aging, osteoporosis, and menopause status in women (4, 16, 17).

Griffith et al. reported that the marrow fat content was increased and perfusion was reduced in the L3 body of elderly men and women with osteopenia and osteoporosis compared to those with normal BMD according to MR spectroscopy and dynamic contrast enhancement. Reduced perfusion in osteoporosis due to the functional impairment of intra-osseous vessels such as atherosclerotic change was considered as a cause of increase in bone marrow fat fraction (1, 3). Tang et al. also indicated that an increase in the

marrow fat content of the L3 body was related to decreases in the bone density and apparent diffusion coefficient (ADC) in postmenopausal women. Reduced diffusion in extracellular water molecules may be caused by an increase in the space between the bony trabeculae occupied by fat or by the lack of water in the yellow marrow in association with aging (4). However, most of the previous studies indicated that there was only modest correlation between bone marrow fat fraction and BMD in both sexes ($r = -0.32$ in male and $r=-0.356$ in female). In addition, the significant difference of fat fraction was not identified between the female subjects with osteopenia and those with normal bone density (1, 3). Thus the exact relationship between vertebral marrow fat and bone density remains unclear and needs to be elucidated.

Although MR spectroscopy is considered the most accurate MR technique for quantification of the fat, it is generally not recommended because for time-consuming. In addition, MR spectroscopy is often performed on only one vertebral body, rendering this technique relatively unreliable. Unlike BMD on DXA, fat content measured on one lumbar vertebral body may not accurately reflect the overall fat content of all lumbar vertebral bodies (1, 3, 4).

In contrast, chemical shift MR imaging is a robust and convenient method for the quantification of fat (6). Multiple lumbar vertebral bodies can be analyzed with this technique in a short amount of time. Therefore, direct side by side analysis between BMD and mean vertebral marrow fat content is possible. Mass et al. reported that Dixon QCSI had excellent reproducibility for measuring the bone marrow fat fraction in the L1-L3 bodies as our study (12). Dixon QCSI has been used for the quantification of bone marrow fat in patients with metabolic, inflammatory, traumatic, and neoplastic disorders (18–20).

Ishijima et al. reported (21) that the changing pattern of marrow composition of L1-L3 bodies in men differs from that in the women. In a study using chemical shift MRI, there was a sharp increase in the fat fraction before the age of 25 in male subjects but no increase thereafter. In contrast, a rapid increase in the fat fraction occurred after the age of 45 in female subjects. In our study, the youngest male was 25-years-old and the youngest female was 35-years-old. There was a significant correlation between vertebral marrow fat fraction and age only in the females but

not in the males, similar to the results of the previous study. Liney et al. reported (22) that marrow fat fractions in the L3 body measured using MR spectroscopy revealed a moderate correlation with those measured using chemical shift imaging ($r^2 = 0.504$) in eight healthy subjects. Recently, Gokalp et al. calculated the marrow fat fraction only in the L3 body by measuring signal intensity in the chemical shift MRI in post-menopausal women. And the study concluded that chemical shift MRI is not a reliable technique to determine the presence of osteopenia or osteoporosis in post-menopausal women (7). Our study included both sexes and a wider age group and also measured the marrow fat contents of the L1-L4 bodies. Thus, our study suggests that measurement of the vertebral marrow fat content using chemical shift MRI is not a reliable tool to detect osteopenia in the overall population. In another studies using MR spectroscopy, inverse correlation between bone marrow fat fraction in the L2 vertebral body and BMD was not confirmed as our study, although marrow fat fraction was higher in subgroup with MRI evidence of bone weakness (e.g., Schmorl's node, endplate depression, wedge deformity, or compression fracture) compared with normal group (23, 24). Discordant study results between ours and the previous studies can be explained by the following points. First, there was only modest correlation between the bone marrow fat fraction and BMD in the previous studies. Second, the marrow fat fraction was measured by using different MR techniques between our study and the previous studies (chemical shift MRI versus MR spectroscopy). Third, we excluded vertebral bodies with anterior wedging (n=3) or degenerative change (n=2) from the analysis.

Shen et al. (25) measured the volume of bone marrow fat using whole body MRI. In their study, the volume of bone marrow fat was inversely related to both the whole body BMD and spine BMD in Caucasian women. However, the volume of the bone marrow fat did not include the spinal marrow fat content. In the study, the volumes of the pelvic and total bone marrow fat had a negative correlation with BMD and a positive correlation with age and visceral adipose tissue. In the contrast, there were no significant correlations between the volumes of the pelvic and total bone marrow fat and subcutaneous body fat.

Obesity is an increasingly important public health

issue. Visceral fat is considered an important source of hormones, cytokines, and inflammatory mediators. As a result, an increase in visceral fat is a possible predisposing factor for osteoporosis (26, 27). Multiple previous studies have indicated that the amount of visceral fat had a positive correlation with hepatic fat fraction. This positive correlation is explained by insulin resistance. Therefore, substantial increase in the hepatic fat fraction evaluated by ultrasound or MRI may be an indicator of metabolic syndrome (11, 28, 29). In our study, BMI had a positive correlation with hepatic fat fraction but no significant correlation with marrow fat fraction for either sex. Our study results suggest that BMI and hepatic fat fraction have no significant correlation with vertebral marrow fat fraction. However, further studies are necessary to support this conclusion.

This study has several limitations. First, it was a retrospective study with a small number of enrolled subjects. Second, fat fraction measured using MRI may have inter-scan variability depending on MR scanner type, scan parameters or method of quantification. Accordingly, fat fraction measured using MRI may not be the same as the real fat fraction (13). In addition, MRI is an expensive diagnostic tool, resulting in limited use for the diagnosis and management of osteoporosis. Third, we did not directly measure the amount of visceral fat mass as an indicator of metabolic syndrome. Fourth, this study included only non-obese Asians. Therefore, the study results can not be generalizable to populations of different BMI and ethnicity.

In conclusion, the bone marrow fat fraction calculated using chemical shift MRI does not identify early decreases in BMD, irrespective of gender.

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Dixon 정량 화학적 변위 자기공명영상을 이용한 척추 골수 지방함량과 이중에너지 방사선 흡수법의 BMD 값의 비교

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목적: Dixon 정량 화학적 변위 자기공명영상(QCSI)의 척추 골수 지방함량과 이중에너지 방사선 흡수법 (DXA)를 통한 BMD 값과의 상관성을 알아본다.

대상과 방법: QCSI와 간의 화학적 변위영상을 포함한 전신 자기공명영상(MRI)과 요추의 DXA를 시행한 68명의 건강한 사람들(평균연령, 50.7세; 범위, 25-76세; 남/여=36/32)을 대상으로 후향적 연구를 시행하였다. 성별과 T-score에 따라 정상(남/여=27/23)과 골감소증(남/여=9/9)집단으로 나누고, MRI로 척추골수와 간의 지방함량을 측정하였다. 각 집단의 나이, 체질량지수(BMI), 골수 지방함량과 간의 지방함량을 비교하였고, 여성에서는 폐경 전후 각 변수들의 비교를 추가하여 Spearman's 상관계수로 평가하였다.

결과: 남성의 나이, BMI, 척추 골수와 간의 지방함량은 정상과 골감소증 집단 사이에 큰 차이를 보이지 않았다. 여성에서는, 골감소증 집단의 평균 나이가 정상집단에 비해 높았고($p=0.01$), 폐경된 경우가 많았으나(폐경 전, 26.1%(6/23); 후, 77.8%(7/9); $p<0.05$), 다른 변수들은 유의한 차이를 보이지 않았다. 골수 지방함량과의 비교에 있어 여성의 나이는 유일한 의미 있는 변수였다($r=0.43$, $p<0.05$).

결론: Dixon QCSI를 통한 척추 골수 지방함량의 측정은 남녀 모두에 있어 DXA BMD 감소를 정확히 반영하지는 않는다.

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