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SHORT COMMUNICATION

Clinical usefulness of the mDIXON Quant the method for estimation of the salivary gland fat fraction: comparison with MR spectroscopy

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Objective: To estimate the fat fraction (FF) in the salivary glands (SGs) by the mDIXON method and the ¹H-MR spectroscopy (MRS) method, and to compare the results.

Methods: 16 healthy volunteers were enrolled. mDIXON Quant and MRS (point-resolved spectroscopy: PRESS) with a single TE were employed to measure the FF in the parotid gland (PG) and submandibular gland (SMG). Multiple TEs were applied in 10 volunteers to correct for T₂ decay. In addition, we assumed that the 1.3 ppm peak accounted for 60% of the total fat peak and estimated the FF (MRS all) as a gold standard. On mDIXON Quant images, volumes of interest were set on the bilateral SGs and we obtained the FF (mDIXON) of each volume of interest.

Results: There was a strong correlation between the results of the mDIXON Quant method and the MRS

(single TE) method ($R^2 = 0.960$, slope = 0.900). Using PRESS with multiple TEs, there was also a strong correlation between FF (mDIXON) and FF (MRS all) ($R^2 = 0.963$, slope = 1.18). FF (MRS all) was 24.9±12.7% in the PG and 4.5±3.0% in the SMG, while FF (mDIXON) was 29.4±16.2% in the PG and 6.4±4.7% in the SMG. There were no significant differences between the two methods, but the Bland-Altman plot showed that FF (mDIXON) was slightly larger than FF (MRS all) for small FF areas.

Conclusion: The mDIXON Quant method could be clinically useful for evaluating the FF of SGs, but the absolute values need careful interpretation.

Advance in knowledge: This study suggested the potential clinical usefulness of the mDIXON Quant method for the SGs.

INTRODUCTION

Hepatic accumulation of triglycerides causes nonalcoholic fatty liver disease, which comprises a wide spectrum extending from simple hepatic steatosis to end-stage liver disease. As a substitute for invasive biopsy, ¹H-MR spectroscopy (MRS) has been widely used to estimate the proton density fat fraction (FF) and it has proven to be a sensitive biomarker for estimating the hepatic triglyceride content.¹⁻³

Fat deposition in the salivary glands is considered to be a characteristic feature of Sjögren's syndrome and its assessment is useful for differentiation from xerostomia due to other causes. Although subjective and semi-quantitative analyses of fat deposition in Sjögren's syndrome have already been performed,^{4,5} there have been no reports about quantitative FF analysis.

MRS has been widely used for estimation of the hepatic FF and is recognized as the gold standard for proton density

FF estimation. However, this method does not provide morphological information and the scanning time is relatively long.

Recent advances in three-dimensional Dixon methods have led to the development of rapid, robust and quantitative approaches that can accurately characterize fat and water contents.

If the longitudinal relaxation is sufficient, the signal intensity can be described as follows:^{6,7}

$$s(t) = \left(W + F \sum a_i \cdot e^{j2\pi t(\Delta f_i)} \right) e^{j2\pi t\psi - (t/T_2^*)}$$

where $s(t)$ represents the signal acquired at time t in a given voxel, Δf_i and a_i are the chemical shift spectral frequency and relative amplitude of the i th spectral peak of F relative to W , ψ represents magnetic field inhomogeneity, and T_2^* characterizes transverse relaxation and

intravoxel dephasing of the signal. The unknown parameters (W , F , ψ and T_2^*) are solved with six measurements of $s(t)$. This method for quantification of fat–water separation is known as the iterative decomposition with echo asymmetry and least squares (IDEAL) technique. The latest IDEAL techniques employ a six-echo acquisition protocol to estimate the FF by the method outlined above.

This method was initially only available on GE scanners, but a similar method called mDixon Quant has become available on Philips scanners and it can be used to automatically obtain various types of images (water, fat, in phase, out of phase, T_2^* and FF) without off-line processing. Because contiguous axial images are acquired, it is possible to calculate FF at any site within the scanning field.

Previous imaging studies of the liver^{7–9} have revealed a strong correlation between the FF obtained by water–fat signal separation using a volume gradient sequence with multiple TEs (6 echoes in refs. 7 and 8 vs 2 or 3 echoes in ref. 9) and the FF obtained by MRS. However, we found only one report about the accuracy of determining the FF in the salivary glands using the 6-echo mDixon method with off-line image processing,¹⁰ while MRS evaluation of the salivary gland FF has not been reported.

Therefore, the objectives of this study were to estimate the salivary gland FF by the vendor-supplied mDIXON Quant method and the MRS method, and to analyse the correlation between these two methods in order to evaluate the efficacy of mDIXON Quant for assessing the fat fraction of the salivary glands because mDIXON Quant is more rapid than MRS and provides additional spatial localization data.

METHODS AND MATERIALS

The institutional ethics review board of Kyushu University Hospital (Fukuoka, Japan) approved this study (approval number 26080). 16 healthy volunteers were enrolled in this study (Table 1). We gave a verbal and written explanation of the purpose of the research, the details of the experiments, and possible adverse effects and risks to the volunteers before we obtained their informed consent. Four volunteers underwent two scans each to evaluate the scan–rescan reproducibility. The two examinations were performed within 3 months of each other.

MR imaging protocol

All MR examinations were done with a clinical 3T whole body MRI system (Ingenuia 3.0 T; Philips Healthcare, Best, the

Netherlands) using a head/neck coil and a torso coil. Two types of MRI sequences, mDIXON Quant and single voxel MRS (point resolved spectroscopy: PRESS), were employed to measure the FF in the parotid gland (PG) and the submandibular gland (SMG). In this preliminary study, we applied PRESS due to the high signal-to-noise ratio because the selected volumes of interest (VOIs) were much smaller than those used in previous liver studies. PRESS was performed with the following parameters: TR = 5000 ms, 1024 samples, spectral band width (Hz) = 2000 and readout duration = 512 ms. To avoid T_1 saturation, a long TR of 5000 ms was applied.

A single TE with 50 ms was applied in all 16 volunteers (32 PGs and 32 SMGs), while multiple TEs were applied in 10 out of 16 volunteers to correct for T_2 decay. To limit scanning time, only the right PG and right SMG (10 PGs and 8 SMGs) were evaluated. VOIs were carefully positioned in the salivary glands and attention was paid to avoid partial volume contamination of the PG VOIs by the retromandibular vein. The outline of the region of interest (ROI) was set approximately 2 mm inside the border of the salivary gland to reduce contamination of the signal caused by shift of the excitation region between water and fat in the surrounding tissues.

The mDIXON Quant method employs a six-echo 3D gradient echo sequence and was performed with the following parameters: TR = 10 ms, TE1 = 1.3 ms, Δ TE = 1.0 ms, fly back = none, echo train length = 6, water fat shift = 0.309 pixels, FOV = 230 × 230 mm, acquisition matrix size = 1.5 × 1.5 mm, reconstruction matrix size = 0.6 × 0.6 mm, slice thickness = 2 mm and total imaging time = 2 min 49 s. To avoid T_1 saturation, a very low flip angle of only 3° was applied.

Data analysis

Calculation of FF by MRS

Determination of the FF by MRS requires estimation of the fat peak and water peak areas, as well as correction by the T_2 value of each peak. To achieve accurate measurement, this should be done for all fat peaks, but quantification of small peaks is difficult and not so robust. We assumed that the 1.3 ppm peak accounted for 60% of the total fat peak,^{1,8} and processing was done as follows.

Post-processing of the spectroscopic data acquired from each volunteer was performed with the vendor's post-processing package. Phase adjustment was done manually, as was spectral shift of the display before integration. The major lipid peak (1.3 ppm) and water peak (4.7 ppm) integrals were obtained.

MRS with a single TE of 50 ms was performed in all 16 volunteers (32 PGs and 32 SMGs). From the data thus obtained, FF (1.3 ppm)_{TE50} was estimated using the following formula:

$$\text{FF (MRS 1.3 ppm)}_{\text{TE50}} (\%) = \frac{\text{fat (1.3 ppm)}_{\text{TE50}}}{\text{water}_{\text{TE50}} + \text{fat (1.3 ppm)}_{\text{TE50}}} \times 100$$

MRS with multiple TEs was performed in 10 volunteers (10 PGs and 8 SMGs) (Figure 1). The T_2 relaxation times of the

Table 1. Characteristics of the volunteer

Number	16
Sex (male, female)	9, 7
Age (years)	37.6 ± 10.0
Height (cm)	166.5 ± 9.7
Weight (kg)	61.4 ± 13.0
BMI	22.0 ± 3.3

BMI, body mass index.

Figure 1. Plots of TE series of PRESS-localized MR spectra (TR/TE₁₋₅ 5000/40, 50, 60, 70 and 80 ms from the volumes of interest. Both the water and fat peaks decrease along with an increase of TE, but the water peak shows more rapid attenuation than the fat peak.

water and fat peaks were determined by separate mono-exponential fitting of the respective spectral line integrals, with the intercepts of the regression lines corresponding to the proton density of water or fat. Then the proton FF (1.3 ppm) was estimated with the following formula:

$$\text{FF (MRS 1.3 ppm) (\%)} = \frac{\text{PD (fat 1.3 ppm)}}{\text{PD (water)} + \text{PD (fat 1.3 ppm)}} \times 100$$

Although we did not determine the ratio of the 1.3 ppm peak to the total fat peak, many reports have indicated that the 1.3 ppm peak accounts for approximately 60% of the total fat peak^{1,8}. Therefore, we assumed it was 60% and recalculated the FF (MRS all), which was defined as the gold standard.

Calculation of FF by the mDIXON Quant method

On mDIXON Quant images, VOIs were set on both sides of the PGs and SMGs using the FF map obtained with MRS to obtain the FF (mDIXON) of each VOI consistent with the VOIs on MRS images.

These procedures were performed by a single head and neck radiologist with 9 years of experience using ImageJ software (National Institutes of Health, Bethesda, MD) (Figure 2).

Statistical analysis

Single regression analysis and Bland-Altman plots were used for comparison of the different methods of calculating FF values. We

Figure 2. FF maps of the PG (a) and SMG (b) obtained by the mDIXON Quant method. (arrows) PG, parotid gland; FF, fat fraction; SMG, submandibular gland.

performed linear regression analysis on all data from PGs and SMGs. The paired t -test was used for comparison between the T_2 of the water peak (4.7 ppm) and that of the fat peak (1.3 ppm). Regarding the scan-rescan reproducibility, we calculated intra-class correlation coefficients (ICC). Analyses were performed with the JMP statistical software package (version 9.0.0; SAS Institute, Cary, NC).

Table 2. The means and the standard deviations for the FF (%) (single TE)

FF (%)	PG ($n = 32$)	SMG ($n = 32$)
MRS 1.3 ppm $_{TE=50}$	30.0 ± 16.1	3.7 ± 2.9
mDIXON	30.7 ± 13.7	5.9 ± 4.9

FF, fat fraction; MRS, ^1H -MR spectroscopy; PG, parotid gland; SMG, submandibular gland.

RESULTS

The means and the standard deviations for the FF (%) and T_2 values (ms) are summarized in Tables 2 and 3.

With a single TE, the mean FF (%) obtained by MRS (1.3 ppm $_{TE=50}$) was $30.0 \pm 16.1\%$ in the PG and $3.7 \pm 2.9\%$ in the SMG, while the results obtained with the mDIXON method were $30.7 \pm 13.7\%$ and $5.9 \pm 4.9\%$, respectively. There was no significant difference of FF (%) between the two groups (PG: $p = 0.555$, SMG: $p = 0.106$).

The salivary gland fat fraction showed a strong correlation between the mDIXON Quant method and the MRS (single TE) method ($R^2 = 0.960$), with a slope ($\pm$ standard deviation) of

Table 3. The means and the standard deviations (SD) for the FF (%) and T_2 values (ms) (multiple TEs)

		FF (%)			T_2 (ms)	
Salivary gland	Case No.	MRS 1.3 ppm with T_2 correction	MRS all	mDIXON	water	fat
PG	1	8.8	13.9	16.0	39.8	75.3
	2	13.6	20.8	19.7	42.1	94.7
	3	30.7	42.4	49.5	35.8	92.2
	4	6.6	10.5	11.0	39.8	77.2
	5	6.9	10.9	15.6	35.2	79.2
	6	33.5	45.6	53.1	39.5	91.8
	7	12.1	18.6	17.5	32.4	90.9
	8	25.7	36.6	50.1	37.9	54.4
	9	15.0	22.8	33.4	53.4	86.1
	10	18.0	26.8	27.8	49.8	104.5
mean $\pm$ SD		17.1 ± 9.7	24.9 ± 12.7	29.4 ± 16.2	40.6 ± 6.5	84.6 ± 13.9
SMG	1	0.7	1.2	1.7	53.7	75.6
	2	4.7	7.5	9.9	42.1	66.0
	3	2.2	3.6	3.8	52.9	80.1
	4	1.5	2.5	4.6	56.7	97.6
	5	5.9	9.5	14.6	46.4	75.6
	6	4.1	6.6	10.6	52.6	79.6
	7	1.8	2.9	2.9	63.6	73.8
	8	1.5	2.4	3.3	41.7	103.6
mean $\pm$ SD		2.8 ± 1.9	4.5 ± 3.0	6.4 ± 4.7	51.2 ± 7.5	81.5 ± 12.7

FF, fat fraction; MRS, ^1H -MR spectroscopy; PG, parotid gland; SMG, submandibular gland.

Figure 3. Correlation between FF (mDIXON) and FF (MRS 1.3 ppm)_{TE=50}. Scatter plot displaying individual results and linear regression (solid line) with Pearson's correlation coefficient ($R^2 = 0.960$), with a slope ($\pm$ standard deviation) of 0.900 ± 0.02 ($p < 0.0001$) and an intercept of 3.08 ± 0.56 ($p < 0.0001$). FF, fat fraction; MRS, ^1H -MR spectroscopy.

0.900 ± 0.02 ($p < 0.0001$) and an intercept of 3.08 ± 0.56 ($p < 0.0001$) (Figure 3).

When PRESS was done with multiple TEs, the T_2 value of the fat peak (1.3 ppm) was significantly higher than that of the water peak (Figure 4) ($p = 0.000$ (PG), $p = 0.001$ (SMG), paired t -test). After taking T_2 decay into consideration, the mean FF (%) obtained by MRS (1.3 ppm with T_2 correction) was $17.1 \pm 9.7\%$ in the PG and $2.8 \pm 1.9\%$ in the SMG. Moreover, when we assumed that the 1.3 ppm peak accounted for 60% of the total fat peak, MRS (all) was $24.9 \pm 12.7\%$ in the PG and $4.5 \pm 3.0\%$ in the SMG, while the mDIXON method gave values of $29.4 \pm 16.2\%$ in the PG and $6.4 \pm 4.7\%$ in the SMG. There was no significant difference between MRS (all) and MRS (mDIXON) (PG: $p = 0.143$, SMG: $p = 0.195$).

There was also a strong correlation between FF (mDIXON) and FF (MRS all) ($R^2 = 0.963$), with a slope ($\pm$ standard deviation) of 1.18 ± 0.06 ($p < 0.0001$) and an intercept of 0.487 ± 1.20 ($p = 0.6904$) (Figure 5a). Bland-Altman plots showing the

difference between them [Bias = 3.18, SD = 0.92, 95% confidence interval (CI) (1.24–5.12), $p = 0.0029$] (Figure 5b).

Regarding the scan–rescan reproducibility, the difference between two measurements of FF (MRS 1.3 ppm)_{TE50} was 1.05–1.3% (95% CI [–3.1–5.1]) and the difference between two measurements of FF (mDIXON) was 0.08–0.85% (95% CI [–2.6–2.7]). Furthermore, based on the number of ICC, the FF (MRS 1.3 ppm)_{TE50} ICC was 0.988 and mDIXON ICC was 0.998; so the reproducibility of these techniques was considered to be quite good.

DISCUSSION

There have been a few reports about proton density FF of the PG, which have demonstrated that the parotid fat content obtained using Dixon's method is positively correlated with both age and BMI in healthy adults.¹¹ However, to the best of our knowledge, only one attempt has been made to assess the feasibility of applying Dixon's method to the salivary glands.¹⁰ Chang et al. compared FFs obtained by the T_1 method, T_2 method and Dixon method. With the T_1 and T_2 methods, they calculated the FF from the signal intensity ratio between non-fat-saturated images and frequency selective fat-saturated images, but this approach has the major drawback of being vulnerable to B_0 and B_1 inhomogeneity. MRS has not previously been employed for estimation of the salivary gland FF, although it has been identified as the gold standard for estimating hepatic FF. Therefore, we first performed PRESS to obtain gold standard data.

Although FF (mDIXON) and FF (MRS 1.3 ppm) were closely correlated without T_2 correction, the T_2 of the fat peak was much longer than that of the water peak in the multiple TE study, and the T_2 values of both water and fat were similar to those previously reported for the liver.¹²

With T_2 correction, FF (mDIXON) and FF (MRS 1.3 ppm) were also strongly correlated. While multipoint analysis is theoretically preferable to single-point analysis, small peaks other than the main ethylene peak were difficult to quantify, especially with long TEs (Figure 1).

Kukuk et al.⁸ determined FF values in patients with fatty liver by both the Dixon and MRS methods, and reported that a close correlation was noted between them and that the methylene peak was over 60%

Figure 4. T_2 values of the water and fat peaks. In both the PG and the SMG, T_2 values of the fat peak are longer than those of the water peak. PG, parotid gland; SMG, submandibular gland.

Figure 5. (a) When the FF was recalculated after assuming that the methylene peak accounted for 60% of the total fat peak, there was a strong correlation between FF (mDixon) and FF (MRS all) ($R^2 = 0.963$), with a slope ($\pm$ standard deviation) of 1.18 ± 0.06 ($p < .0001$) and an intercept of 0.487 ± 1.20 ($p = 0.6904$). (b) Bland-Altman plots showing the difference between them (Bias = 3.18, SD = 0.92, 95% CI [1.24–5.12], $p = 0.0029$). The dotted lines indicate ± 2 SD. FF, fat fraction; MRS, ^1H -MR spectroscopy.

(0.62) of the total fat peak, while Hamilton et al¹ obtained a value of 0.64. By assuming that the methylene peak accounted for 60% (0.6) of the total fat peak, we calculated the FF (MRS all) and defined it as the gold standard. FF (mDIXON) was strongly correlated with FF (MRS all) in our study ($R^2 = 0.963$, slope = 1.18). The reason why the slope is 1.18 (more than 1) might be associated with the assumption that the methylene peak accounted for 60% of the total fat peak. Another likelihood is the problem associated with the fitting of MRS. Especially, the 5.3 ppm fat peak ($-\text{CH}=\text{CH}$) and 4.2 ppm fat peak ($-\text{CH}_2\text{O}-\text{CO}-$) are affected by the water peak due to close proximity of the water peak.

Since the slope is 1.18, Bland-Altman plots showed a proportional bias. Moreover, it demonstrated that FF (mDIXON) was a little larger than FF (MRS all) in the small FF area, which may be associated with the effect of noise on the estimation of FF (mDIXON).⁶

In spite of such a discrepancy, the mDIXON Quant method is a sophisticated quantification method that provides both the FF and anatomical information. In addition, the reproducibility of this technique was considered to be quite good, because ICC was 0.998. Therefore, the mDIXON Quant method can potentially be employed for diagnostic imaging and it is considered to have a higher clinical usefulness than MRS.

The present study had several limitations. First, we performed MRS with fitting to a single fat peak (the methylene peak). In the future, we plan to use STEAM acquisition instead of PRESS, which will make it possible to employ shorter TEs and lessen the effect of J coupling.¹²

Second, shift of the excitation region between water and fat in the surrounding tissues causes contamination of the signal, but we set the ROI approximately 2 mm inside the border of the salivary gland to reduce such contamination and we considered that this effect was negligible.

Third, in this preliminary study, we combined the data for PGs and SMGs due to the small number of volunteers enrolled. However, the fat content of both glands is thought to be similar, so the effect of combining these data should be trivial. To clarify this point, further analysis will be needed in a larger number of subjects.

CONCLUSIONS

Taking into consideration T_2 decay and the ratio of the 1.3 ppm peak to the total fat peak, we obtained the FF (MRS all) as a gold standard. FF (mDIXON) and FF (MRS all) values showed a strong correlation, with no significant difference between them. However, the Bland-Altman plot showed that FF (mDIXON) was slightly larger than FF (MRS all) when small FF areas were measured. Therefore, the mDIXON Quant method could be clinically useful for evaluating the salivary gland fat fraction, but the actual values need to be interpreted carefully.

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