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Hepatic fat and adenosine triphosphate measurement in overweight and obese adults using ^1H and ^{31}P magnetic resonance spectroscopy

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Abstract

Background/Aims—Magnetic resonance spectroscopy (MRS) measures hepatic fat and adenosine triphosphate (ATP), but magnetic resonance studies are challenging in obese subjects. We aimed to evaluate the inter- and intrarater reliability and stability of hepatic fat and ATP measurements in a cohort of overweight and obese adults.

Methods—We measured hepatic fat and ATP using proton MRS (^1H MRS) and phosphorus MRS (^{31}P MRS) at baseline in adults enrolled in the Action for Health in Diabetes (Look AHEAD) clinical trial at one site. Using logistic regression, we determined factors associated with successful MRS data acquisition. We calculated the intra- and inter-rater reliability for hepatic fat and ATP based on 20 scans analysed twice by two readers. We also calculated the stability of these measures three times on five healthy volunteers.

Results—Of 244 participants recruited into our ancillary study, 185 agreed to MRS. We obtained usable hepatic fat data from 151 (82%) and ATP data from 105 (58%). Obesity was the strongest predictor of failed data acquisition; every unit increase in the body mass index reduced the likelihood of successful fat data by 11% and ATP data by 14%. The inter- and intrarater reliability were excellent for fat (intraclass correlation coefficient = 0.99), but substantially more variable for ATP. Fat measures appeared relatively stable, but this was less true for ATP.

Conclusions—Obesity can hinder ^1H and ^{31}P MRS data acquisition and subsequent analysis. This impact was greater for hepatic ATP than hepatic fat.

Keywords

^1H and ^{31}P magnetic resonance spectroscopy; liver ATP; nonalcoholic fatty liver

Hepatic magnetic resonance spectroscopy (MRS) is increasingly being applied to many areas of patient-oriented liver research (1). Proton MRS (^1H MRS) can quantify triglyceride

content in the liver (2) and has become well-established for this purpose (3). Phosphorus MRS (^{31}P MRS) can evaluate complex metabolic processes *in vivo* and has been applied to many areas of clinical liver research, including investigations of cirrhosis, hepatitis, obstructive jaundice and hepatic energy homeostasis (4–7). MRS uses standard magnetic resonance equipment, is noninvasive and imparts little risk on study subjects. Further, the data generated by ^{31}P MRS are unique. For example, no other research modality can assess hepatic energy *in vivo* as indicated by hepatic adenosine triphosphate (ATP) levels.

Despite these important attributes, some obstacles are faced by investigators interested in human hepatic MRS. Human hepatic MRS protocols, in particular ^{31}P MRS protocols, can be technically challenging, time consuming and costly. There is considerable variation in data analysis techniques in the published literature, and all share the potential for systematic and random error (8). Perhaps most important, the reported intra- exam and intrasubject variability ranges widely in published studies (9,10). Furthermore, the effect of fasting or time of day on hepatic ATP levels is uncertain.

Accordingly, it is important to understand the technical factors associated with cost-efficient and successful MRS data acquisition and analysis. In this paper, we report our experience with both hepatic ^1H and ^{31}P MRS in a cohort of overweight and obese diabetic subjects enrolled in the Action for Health in Diabetes (Look AHEAD) study compared with healthy controls. We also report inter- and intra-observer variability in the evaluation of spectra, and the stability of MRS measurements through repeated examinations on healthy volunteers. We hypothesized that we could successfully complete ^1H and ^{31}P MRS in a reliable fashion in obese adults.

Patients and methods

Patients

We evaluated subjects enrolled in an ancillary study of fatty liver disease at one site of the Look AHEAD trial. Look AHEAD is a multicentre, randomized controlled trial of weight loss interventions to assess the long-term effects of an intensive weight loss intervention among overweight and obese adults (age 45–75 years) with type 2 diabetes on cardiovascular morbidity and mortality. Participants were recruited if they had a body mass index (BMI) $\geq 25 \text{ kg/m}^2$ ($\geq 27 \text{ kg/m}^2$ if on insulin), but excluded if their body weight was > 350 pounds. The study design and inclusion and exclusion criteria have been described in detail elsewhere (11). As a part of both the parent Look AHEAD trial and our ancillary study, subjects underwent extensive data collection, including questionnaires, physical measurements and blood assays. For our single-centre fatty liver ancillary study, we also measured hepatic fat using ^1H MRS and hepatic energy using ^{31}P MRS. Subjects were enrolled and studied at baseline between January 2002 and April 2004. In addition, repeat measurements for reproducibility were performed on five healthy volunteers, with a mean BMI of 25.

Magnetic resonance spectroscopy protocol

Localized MRS was carried out on a 1.5T whole body scanner (Philips Gyroscan ACS-NT; Philips Medical Systems, Best, the Netherlands). Subjects were in the supine position with a 14 cm ^{31}P transmit/receive surface coil placed on the lateral surface of the body close to the liver. The position of the coil was verified on T_1 -weighted spin echo localizer and images were acquired in axial, coronal and sagittal orientations. Small markers filled with water were attached to the surface coil and the patient's chest to guide the placement of the surface coil. Magnetic field homogeneity was adjusted automatically on the water ^1H resonance frequency. First, a ^1H MR spectrum of the volume of interest (VOI, $60 \text{ mm} \times 50 \text{ mm} \times 60$

mm in the anterior–posterior, right–left and head–foot directions respectively) was acquired using the PRESS technique [repetition time (TR) = 10s, echo time=30 ms, four averages, spectral width 1000 Hz and 1024 data points] without water suppression (12). A ^{31}P spectrum was collected from the same VOI using the ISIS technique with proton decoupling (TR = 2.4s, 128 acquisitions, spectral bandwidth of 1500 Hz and 512 data points). An adiabatic pulse with tanh modulation was used for excitation (13).

Proton magnetic resonance spectra were processed in the frequency domain using an in-house software 'csx' (14). Water/fat ratio was determined by integration of the respective signals after zero filling to 2048 data points and exponential broadening of 3 Hz. Because preliminary analyses demonstrated poor intra- and inter-rater reliability for ATP using csx, we switched to a circle-fitting (CFIT) programme (15) for the ^{31}P spectra. This approach uses real and imaginary components as a continuous circular trajectory, which improves the stability of the estimation process and reduces some of the subjective input into the zero and first-order phase correction and baseline correction. ^{31}P spectra were processed as follows: the free induction decay was zero filled to 8192 data points and exponential broadening of 15 Hz was applied. After Fourier transformation, a zero and first-order phase correction was applied.

Hepatic ^{31}P MRS results in six resonance signals: phosphomonoesters; inorganic phosphate; phosphodiesteres; and the nucleotide triphosphates, including γ , α and β signals resolved sequentially. These latter three peaks are commonly referred to as ATP signals, although uridine, guanosine, inosine and cytosine triphosphates contribute to these signals as well (16). Most published ^{31}P MRS research expresses 'hepatic ATP' as β -ATP/total phosphorus, because the γ and α signals may include adenosine diphosphate.

Analyses

Determining 'successful' magnetic resonance—The assessment of fat and ATP was not successful in all cases. A single reader (rater 1) determined whether the spectra were acceptable for ATP measurement. We used bivariate logistic regression to determine whether participant factors, including weight, BMI, waist circumference, age, race and gender, were associated with successful ^1H and ^{31}P MRS ATP separately.

Intra- and inter-rater reliability—To assess intra- and inter-rater reliability, 20 subjects from Look Ahead were randomly identified among those who had successful ^1H and ^{31}P MRS. Two raters blinded to each other and prior readings read these 20 scans twice for hepatic fat (using csx) and ATP (using CFIT). The raters separated their repeat readings by > 1 month. Results were then compared, and the intraclass correlation coefficient (ICC) was calculated for each.

Reproducibility and stability over time—To assess the reproducibility and stability of both fat and ATP over time, five healthy volunteers without known liver disease underwent ^{31}P MRS three times:

- i. Day 1 am, fasting.
- ii. Day 1 pm, nonfasting.
- iii. Day 2 am, fasting.

Hepatic fat and ATP were estimated by rater 1. We calculated an ICC to compare fasting levels from both days, and compared it with the nonfasting level.

All statistical analyses were conducted using STATA 8.2 (STATA, College Station, TX, USA).

Results

Acquisition of successful ^1H and ^{31}P magnetic resonance spectroscopy

Two hundred forty-four subjects agreed to participate in our fatty liver ancillary study out of 318 subjects in the Johns Hopkins site of the Look AHEAD Study (77%), and 185 consented to MR. The enrolment and completion of MR testing is shown in Figure 1. There were no significant differences between the 244 subjects who agreed to participate in our ancillary study and the 185 who additionally agreed to have MR (data not shown). Of the 185 who consented, we were able to obtain successful ^1H MRS for liver fat in 151 (82%) and ^{31}P MRS for ATP in 105 (58%). The most common reason for failure to get MR data on fat was participant claustrophobia and inability to fit in the scanner. The most common reason for failure to get MR data on ATP was poor signal-to-noise ratio (SNR; Fig. 2) of the spectra. In many instances, we observed that an increased distance between the surface coil and the VOI was associated with failure to obtain acceptable SNR in ^{31}P MR spectra. A threshold seemed to exist around 60 mm; those with a distance > 60 mm yielded only two acceptable ^{31}P MR spectra, whereas nearly one third of those with unacceptable SNRs with valid distance data (8/28) were above this threshold ($\chi^2 = 11.3$, $P = 0.001$). Technical failures, which include malfunction in the transmit/receive coil and lost computer files (two), also contributed to unsuccessful data collection for fat and ATP.

Factors associated with successful ^1H and ^{31}P MRS are shown in Table 1. Overall, we found that the strongest predictor of unsuccessful MR testing was obesity, as measured by weight, BMI or waist circumference. We found that, for every one unit increase in BMI, participants were 11% less likely to have a successful MR for fat ($P = 0.001$) and 14% less likely to have a successful ^{31}P MR reading ($P = 0.001$).

Our experience confirmed these findings. We observed that obese participants may be less likely to tolerate MR examinations; some were unable to lie flat, reported back pain or experienced difficulty positioning themselves in the narrow scanner bore. Because of large abdominal girth, some were required to extend their arms above their heads so that the surface coil could be properly positioned. Because the ^{31}P MRS acquisition sequences occurred after the anatomic MRI and the ^1H MRS scans, some subjects simply fatigued. At times, the surface coil position required multiple adjustments, further lengthening the exam. A number of participants described claustrophobia either immediately before or just after their examination began, resulting in cancellation of the study.

Finally, African-American women were less likely to complete a successful ^{31}P MR. When accounting for an interaction between race and gender, African-American women had an 87% decreased odds of successfully completing the ^{31}P MR ($P = 0.04$), after adjusting for BMI.

Reliability, reproducibility and stability over time

^1H magnetic resonance spectroscopy for fat—Two raters independently read the data on 20 subjects chosen randomly from the cohort. This group included 12 men, with a mean age of 60.2 years and a mean BMI of 33.5 kg/m². Overall, the intra- and interreliability for hepatic fat were both excellent. For raters 1 and 2, the intrarater ICC on reread of 20 subjects was 0.99. The inter-rater reliability was also 0.99. Finally, we compared the repeat measures on our five healthy volunteers, who included two men. For all five healthy volunteers, the mean age was 28 and a mean BMI was 25 kg/m². The stability of the fat measures in healthy volunteers at the three time points was excellent (ICC 0.99, Fig. 3 top panel).

³¹P magnetic resonance spectroscopy for adenosine triphosphate—Overall, the intrarater reliability for hepatic ATP was excellent (range 0.83–0.92) and the inter-rater reliability was good [(on average 0.61), Table 2]. Although this appeared to be affected by BMI, when inter-rater averages were compared, the ICC was 0.64 for subjects below the median BMI (32.8 kg/m²) as compared with 0.58 for subjects above the median BMI ($P > 0.40$). The inter-rater ICC improved from the first read to the second read, suggested a 'learning curve' effect. Finally, looking at the repeated measures in our healthy volunteers demonstrated that the ATP measures were also variable at the three times points (Fig. 3 bottom panel). We found the change in ATP levels ranged from 2 to 39% in the fed state and from – 18 to 26% in the fasted state.

Discussion

Our experience has taught us several practical lessons that have been valuable in follow-up studies and may also be valuable to other researchers in the field. Firstly, a considerable proportion (25%) of our participants declined to undergo the MR study. Moreover, a smaller but still sizable number of subjects had an MR exam, but the data were either not obtainable or not usable. This failure was mostly associated with estimates of obesity.

We found that ¹H MRS data were highly reproducible and relatively easy to obtain on most subjects. In contrast, it was more difficult to acquire and process quality ³¹P MRS data on our participants. The single greatest obstacle for the acquisition of data was obesity, which resulted in a poor SNR. Female participants were also less likely to have successful ³¹P MRS, perhaps because of the effect of breast tissue on surface coil placement.

Furthermore, we found that processing the ³¹P data was challenging. The single greatest factor may be that existing software programs share the potential for both random and nonrandom error. We initially used our in-house software 'CSX'. While this software performed well for the ¹H MRS data, reliability was consistently poor for ATP (ICC < 0.20), and accordingly we switched to another program, CFIT, which performed much better. Although CFIT is somewhat more automated than CSX, we still seemed to experience a 'learning curve' effect. We did not find that the sum of γ , α and β signals/total phosphorus improved reliability compared with β signal/total phosphorus using either program. Finally, we found that ATP measures were variable over three time points. We are uncertain how much of this represents true biological variability vs error related to data acquisition or processing.

Despite the clear association between measures of obesity and data acquisition, we found it difficult to predict whether individual patients could be successfully scanned. Use of a 'homemade' styrofoam MR model did not improve the success rate. This situation is perhaps analogous to the application of ultrasound marking for liver biopsies, where it has been shown that bedside examinations and obesity cannot reliably predict landmarks and successful procedures (17). It has been reported that male gender and higher socio-economic standing are related to claustrophobia during MR, and some have suggested the use of screening questionnaire, which we did not use (18,19).

To our knowledge, this is the largest series that has evaluated the feasibility and reproducibility of hepatic energy measurement on overweight and obese subjects using ³¹P MRS. Two previous pilot studies have included few subjects with relatively lower BMI: Cortez-Pinto *et al.* (20) examined eight nonalcoholic steatohepatitis patients (mean BMI 31.0) and Nair *et al.* (21) examined seven overweight healthy volunteers (mean BMI 31.8). Like many published hepatic MRS studies, these papers did not report coefficients of

variation and error. Unfortunately, because even the methodologies are often not described in a uniform manner, comparisons between studies may be difficult or impossible (22).

Our study has several limitations. Firstly, we emphasize that our fatty liver study was an ancillary to the parent Look AHEAD study and that other ancillary studies were occurring concurrently. Accordingly, our subjects had multiple lengthy requests for their time. In addition, because of the additional dynamic ATP data we collected, we were unable to use sedatives in our participants. However, this would probably have increased the tolerability of the MR testing for the subjects and could be considered in other studies. Further, our subjects had type 2 diabetes, and therefore our results may not be generalizable to overweight and obese adults without diabetes. Finally, it is unknown, though possible, that study subjects are more likely to report claustrophobia or discomfort than patients presenting for clinical MR. We found that the most important element to successful recruitment into the MR component was excellent rapport generated by the study coordinators and personnel.

Ongoing developments in MR research may improve the potential of ^{31}P MRS research in this patient population. For example, hepatic ^{31}P MRS with an open MR scanner may be feasible, but has not been reported. Further, higher magnetic strength (e.g. 3 T) may improve SNR. While higher magnet strength can indeed improve spectral resolution in MR spectroscopy, research on brain MRS suggests that SNR improvements are small and do not even closely approximate the theoretical 100% improvement from the doubling of magnet field strength (23). At least some of the expected benefit of higher magnet strength is offset by alterations to data acquisition parameters (e.g. because of increasing T1 relaxation times) (24). The optimal hepatic ^1H MRS and ^{31}P MRS protocols at higher magnet strength will need to be defined (25). Finally, further refinements in processing software to limit error would be highly desirable.

Based on our experience, we recommend that investigators examine and report the inter- and intrarater reliability and reproducibility in their studies. Also, we recommend MRS data acquisition occur in as uniform a manner as possible in regard to time of day and time since last food consumption.

In conclusion, ^1H MRS for hepatic fat measurement is easy to obtain, has a reasonable success rate that is similar to rates reported for clinical MR studies (26) and is highly reproducible. ^{31}P MRS, however, can be challenging, especially among more obese study subjects. Despite these difficulties, however, we feel that these novel data will prove useful. ^{31}P MRS is a novel and noninvasive means to study complex *in vivo* biochemical processes, and it may be most valuable in subjects with abnormal metabolic processes, including obesity. Newer developments, such as open MR, higher field strength and more fully automated data processing software, may enable even greater success with MRS in the future.

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Fig. 2.

Top panel: Example of an adenosine triphosphate (ATP) spectra with unacceptable signal-to-noise ratio (SNR). Bottom panel: Example of an ATP spectra with acceptable SNR and signals labelled: phosphomonoesters(PME); Inorganic phosphate (PI); phosphodiesters (PDE); γ , α and β ATP.

Fig. 3. Reproducibility and stability of ^1H and ^{31}P magnetic resonance measures in five subjects without known liver disease at three time points.

Univariate analysis of factors associated with successful proton and ³¹P magnetic resonance spectroscopy data acquisition

Table 1

	Consented for MR (n = 185)	Successful ¹ H MRS (n = 151)	Odds ratio (P-value)	Successful ³¹ P MRS (n = 105)	Odds ratio (P-value)
Female (%)	51	54	1.65(0.19)	47	0.47(0.03)
African American (%)	31	34	3.05(0.03)	30	0.53(0.08)
Age (years)	60.9(6.2)	60.2(6.7)	1.04(0.25)	61.7(6.9)	1.05(0.07)
Height (cm)	170(9.2)	169(9.0)	0.96(0.04)	169(9.0)	1.01 (0.58)
Weight (kg)	103(18.4)	100(16.7)	0.95 (< 0.001)	97.3(16.1)	0.97(0.003)
BMI (kg/m ²)*	35.6(5.8)	34.9(5.1)	0.89(0.001)	33.7(4.55)	0.87 (< 0.001)
Waist circumference (cm)	116(14.1)	114(13.2)	0.95 (< 0.001)	111.4(12.3)	0.95(0.001)

* BMI, body mass index (kg/m²). Data presented are means (standard deviations).

Odds ratio and P-value calculated in reference to those consented for MR.

¹H MRS, proton magnetic resonance spectroscopy; MR, magnetic resonance; ³¹P MRS, phosphorus magnetic resonance spectroscopy.

Table 2

Intraclass correlations for β -adenosine triphosphate as measured by ^{31}P magnetic resonance spectroscopy using the circle-fitting program in 20 randomly selected subjects

Intraclass correlations	Overall	β -ATP by median BMI [*]	
		<32.8 kg/m ²	>32.8 kg/m ²
<i>Intrarater comparison</i>			
Rater 1 (1st) vs. rater 1 (2nd)	0.83	0.78	0.90
Rater 2 (1st) vs. rater 2 (2nd)	0.92	0.88	0.96
<i>Inter-rater comparison</i>			
Rater 1 (average) vs. rater 2 (average)	0.61	0.65	0.58
Rater 1 (1st) vs. rater 2 (1st)	0.39	0.28	0.56
Rater 1 (2nd) vs. rater 2 (1st)	0.65	0.66	0.62
Rater 1 (1st) vs. rater 2 (2nd)	0.51	0.54	0.51
Rater 1 (2nd) vs. rater 2 (2nd)	0.70	0.86	0.56

* Median BMI of the twenty subjects randomly selected for rereads. ATP, adenosine triphosphate; BMI, body mass index.