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Proton magnetic resonance spectroscopy with a body coil in the diagnosis of carcinoma prostate

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Abstract We evaluate the feasibility of proton magnetic resonance spectroscopy (^{1}H MRS) using a spine coil receiver (body coil) in the diagnosis of carcinoma prostate. Seventeen patients with biopsy-proven prostate carcinoma, five patients of benign prostatic hyperplasia (BPH) and five healthy young volunteers underwent ^{1}H MRS investigation. MRS was performed at 1.5 Tesla using a spine receiver coil for signal reception. In vivo citrate levels are reported as a ratio of citrate peak area to the sum of the areas of choline and creatine peak. MRS spectrum with good sensitivity and signal to noise (S/N) ratio was obtained in all 27 subjects. The citrate to creatine plus choline ratio was 0.31 ± 0.25 in patients with cancer, 1.43 ± 0.58 in BPH and 2.16 ± 0.56 in controls. The difference in ratios between cancer and BPH and cancer and control was statistically significant ($p < 0.01$). Within the cancer group, there was a statistically significant decline in levels with higher-grade malignancy ($p < 0.05$). There were no complications of the procedure. There is a statistically significant decline in the ratio of citrate to choline plus creatine in the regions of cancer prostate when compared with BPH or normal control. The study demonstrates that MRS data can be reliably acquired using a spine coil receiver. MRS may also play a role in differentiating well-differentiated tumors from the anaplastic variety.

Keywords Malignancy · Nuclear magnetic resonance · Chemical shift imaging · PSA · Gleason score

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Introduction

Carcinoma prostate is one of the most common malignancies affecting men. Newer minimally invasive and highly effective treatment modalities have shown a definite survival advantage with early diagnosis of the condition [1]. Currently available modalities for diagnosing this condition leave a lot to be desired in terms of accuracy with minimal morbidity [2].

Magnetic resonance spectroscopy (MRS) is one of the newer modalities under evaluation for this purpose. The majority of current literature on MRS for prostatic disease is based on the use of endorectal coils [3, 4, 5, 6, 7]. This is an unpleasant procedure causing significant discomfort for most patients. It is also expensive since endorectal coils are disposable. In this study, we have evaluated the feasibility of carrying out proton magnetic resonance spectroscopy (^{1}H MRS) using a spine coil receiver.

Materials and methods

Seventeen patients with biopsy-proven carcinoma prostate, five patients of benign prostatic hyperplasia (BPH) and five healthy young volunteers underwent ^{1}H MRS of the prostate. The project was approved by the Hospital Ethics Committee and informed consent of the subjects was taken. The diagnosis of malignancy was suspected on the basis of clinical findings on a digital rectal examination (DRE) or elevated serum prostate-specific antigen (PSA) levels and confirmed by a transrectal Tru-cut needle biopsy of the prostate. MRS investigation was carried out 3 weeks or more after the biopsy.

Five subjects had symptomatic BPH (International Prostate Symptom Score 12–18), normal PSA and no evidence of malignancy on DRE. Healthy volunteers were recruited from patients presenting to the clinic with urolithiasis. All volunteers were below 40 years of age and none had any complaint attributable to the prostate. All had a normal PSA value and normal DRE. Volunteers were chosen below the age of 40 years since BPH changes begin to appear in the prostate after this age and we did not want to inadvertently include patients with asymptomatic BPH in this group.

Magnetic resonance imaging (MRI) and MRS were performed at 1.5 Tesla (MAGNETOM, Siemens) using a spine receiver coil for optimal signal reception with the body coil acting as transmitter. Each subject was positioned supine with the pelvic region at the center of the coil. Following scout images, T1-weighted images were acquired in two planes (sagittal and axial) and T2-weighted images in the coronal plane using spin echo and gradient echo sequences, respectively. T2 images were obtained to identify the full extent and irregularity of tumor. Since all the patients were biopsy-proven, large-volume cancer prostate, the hypointense region in T2 image was used for positioning the voxel after ruling out a post-biopsy hematoma on T1 image. Depending on the size of the tumor, voxel of appropriate dimension (5–8 ml) was chosen and positioned well within the tumor for further MRS study.

Volume-localized in vivo proton MRS was carried out using STEAM (Stimulated Echo Acquisition Mode) pulse sequence. Magnetic field homogeneity was achieved at the global and voxel level by shimming on the water resonance. The line width of water signal after shimming on the voxel was typically in the range of 5–10 Hz. Two hundred and fifty-six scans with water suppression were collected using an echo time (TE) of 135 ms and repetition time (TR) of 2.0 s, with a total acquisition time of 8.5 min. Total examination time, including imaging, shimming and spectroscopy, was around 45 min for each patient. The time domain signal (FIDs) was zero filled to 4 K data points with a Gaussian broadening of 4 Hz before Fourier Transformation. Chemical shifts are reported using water as the internal standard at 4.70 ppm. In vivo citrate levels are reported as a ratio of citrate peak area to the sum of the areas of the choline and creatine peak [7, 8, 9].

Results

A good quality MRS spectrum could be obtained in all 27 cases (Fig. 1) and no subject suffered any complication. Of the 17 cancer patients (age range 54–82 years), 11 had a nodule palpable on DRE (65%) while 16 had elevated serum PSA levels (94%). The Gleason score of the tumor on prostate biopsy ranged from 3 to 8 (median 4) while the PSA ranged from 3 to 4,780 ng/ml (Table 1). Citrate to choline plus creatine peak ratio for these patients was 0.31 ± 0.25 (Table 2).

None of the patients of BPH (age 56–77 years) or volunteers (age 34–39 years) had a nodule palpable on DRE and all had a PSA below 1.5 ng/ml. The ratio of citrate to choline plus creatine peak was 1.43 ± 0.58 and 2.16 ± 0.56, respectively (Table 2).

Two patients moved during the data acquisition. MRS spectrum analysis in these two patients revealed a raised citrate to choline plus creatine peak ratios (1.45, 2.0). Since there was a possibility of contamination of spectrum from adjacent normal tissues, these values have not been included in calculating the mean and standard deviation of values for cancer prostate. However, this represents an inherent limitation of the investigation and thus has been included in calculating the sensitivity of the test as false negative.

The ratios obtained in the cancer patients were significantly lower than those in BPH or control ($p < 0.01$). This was true of the cancer patients as a single group and also when separated as two groups based on the Gleason score. Within the cancer group, separation on the basis of the grade of tumor (Gleason score < 7 or ≥ 7) was also possible by MRS at statistically significant levels ($p < 0.05$). None of the patients of BPH or volunteers had a ratio in the malignant range (Fig. 2). The sensitivity of MRS in diagnosing carcinoma prostate was 88% with two false negatives and the specificity was 100% with no false positives.

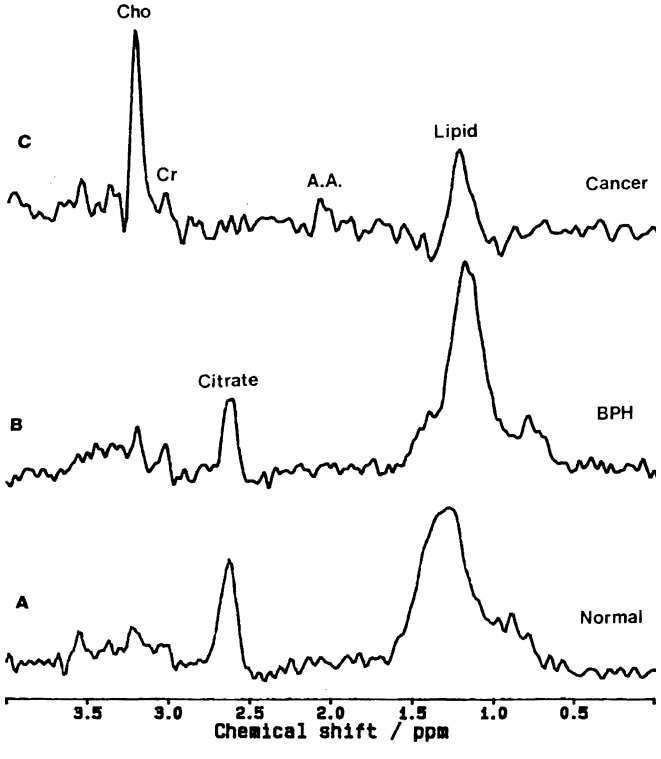

Fig. 1 Representative water suppressed in vivo Proton MR Spectra from (*A*) normal volunteer, (*B*) patient with BPH and (*C*) Cancer prostate. *Cho* Choline, *Cr* Creatine, *AA* Amino acids

Discussion

Carcinoma prostate is one of the most common malignancies diagnosed among men. Screening and early diagnosis are beneficial because 80–90% of men with newly diagnosed carcinoma prostate can be treated definitively [1].

Current modalities for evaluation and diagnosis of prostatic cancer include digital rectal examination (DRE), transrectal ultrasonogram (TRUS), prostate-specific antigen (PSA) and random biopsies of the prostate. DRE misses up to 45% of all cancers subsequently detected on biopsies and cancers detected on DRE are in an advanced stage in up to 50% cases [10]. Using a PSA cut-off value of 4 ng/ml as indicative of carcinoma prostate, up to 25% men with cancer may be missed and the positive predictive value of the test is only 30% in asymptomatic men [10]. Using the endorectal coil, MRI has an accuracy of 54–82%, sensitivity of 51–89% and specificity of 67–87% [1]. The only definitive means of distinguishing prostate cancer from BPH and normal tissue is histologic evaluation of biopsy samples and this is subject to

Table 1 Patient data

Sno.	Age	DRE positive (Y = yes)	PSA (ng/ml)	Gleason score	*Citrate* choline + creatine
Carcinoma prostate					
1	65	N	34	4	1.45
2	60	N	25	4	2.0
3	67	Y	36	7	0.13
4	60	Y	1772	4	0
5	64	Y	346	4	0.79
6	72	N	13	8	0
7	65	Y	3	3	0.53
8	70	Y	55	3	0.31
9	54	N	780	5	0
10	55	Y	26	7	0
11	67	N	56	5	0.42
12	72	N	34	5	0.35
13	72	Y	45	5	0.41
14	82	Y	250	8	0.21
15	60	Y	77	3	0.38
16	65	Y	23	4	0.59
17	74	Y	4780	4	0.6
BPH					
18	70	N	0.1	-	0.92
19	77	N	0.5	-	1.09
20	60	N	0.2	-	2.38
21	56	N	0.1	-	1.59
22	62	N	0.2	-	1.19
Volunteers					
23	39	N	0.1	-	2
24	36	N	0.2	-	1.6
25	34	N	0.2	-	3.1
26	38	N	1.4	-	1.9
27	34	N	0.2	-	2.2

Table 2 Calculated metabolite ratio of citrate / (choline + creatine) for the three categories of patients studied (n = number in each group) together with *p* values and Gleason score

Category	Gleason score	(n)	Citrate/ (choline + creatine) peak area ratio		*P* value cf. control/BPH
Cancer	≥7	4	0.085 ± 0.10 (0–0.21)	0.31 ± 0.25	< 0.01
	< 7	11	0.398 ± 0.24 (0–0.79)		
BPH	–	5	1.43 ± 0.58 (0.92–2.38)		–
Control	–	5	2.16 ± 0.56 (1.6–3.1)		–

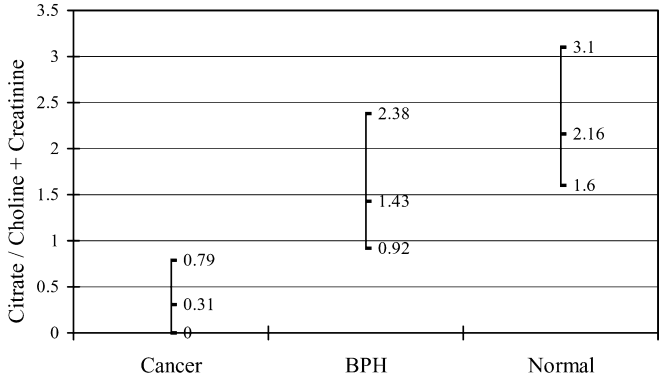

Fig. 2 Citrate/(Choline + Creatine) ratios with mean, minima and maxima of the data obtained in patients with cancer prostate, BPH and normal volunteers

large sampling errors [11, 12]. Thus, there is clearly a need for developing an additional diagnostic modality that satisfies the criteria of being sensitive, specific and non-invasive. There is increasing evidence that MRS may play a role in the diagnosis of carcinoma prostate prior to biopsy or surgery. Single voxel ^{1}H MR spectroscopy studies of the human prostate have been able to discriminate prostate cancer from normal peripheral zone based on reduced citrate and elevated choline in the region of cancer. The value of citrate as a tissue marker for differentiation of BPH from cancer prostate has been demonstrated in animal models, cell lines and tissue extracts [3, 4, 5, 6, 7,13, 14, 15, 16, 17, 18, 19, 20, 21].

Using endorectal MRS, Kurhanewicz et al. [7] noted significantly lower citrate to choline plus creatine ratios in cancer regions (0.67 ± 0.04) compared with

BPH (1.19 ± 0.5) or normal controls (1.5 ± 0.1). There was no overlap between the cancer and control groups. In vitro MRS spectra confirmed these findings with values similar to the in vivo MRS. Wefer et al. [3] found the combined modality of MRI and MRS to have an accuracy similar to that of biopsy for intra prostatic localization of cancer and more accurate than biopsy in the region of the prostatic apex. Similarly, in another study, Schiedler et al. [6]demonstrated the advantage of combining MRI and MRS in increasing the ability to localize prostate cancer.

The use of surface coils has been considered technically difficult because of the small size and deep location of the prostate gland with low signal-to-noise ratio. Similar to a few recent studies using either surface coils or pelvic phase array coils [18, 19], our study, which has been conducted using a spine coil receiver instead of the more usual endorectal coil used by other investigators [3, 4, 5, 6, 7], demonstrates good spectral acquisition.We have obtained clear spectra in all subjects with high signal-to-noise ratio. The predominant finding has been a significant drop in citrate levels in cancerous regions with the ratio of citrate to choline plus creatine peak areas showing statistically significant lower values (0.31 ± 0.25) compared with either BPH (1.43 ± 0.58) or controls (2.16 ± 0.56). These values are similar to those found by other investigators [16, 17] using either the surface coil [14] or the endorectal coil [7]. Kim et al. [15], using external body surface coil MRS, reported consistently lower citrate levels in Ca Prostate compared with BPH and controls. The ratios reported were similar to those reported by endorectal coil imaging. Recently, Kaji et al. [22] evaluated the use of external phased array surface coil versus endorectal coil in 35 patients and concluded that the phased array coil provided detection with accuracy comparable to that of the endorectal coil.

Absence of citrate peak was observed in four cancer patients and a similar observation was reported by Liney et al. [16]. Such low levels can be explained through biochemical studies which have demonstrated a dependence of citrate levels on the degree of differentiation of prostatic adenocarcinoma. These studies show that citrate occurs in low levels in early prostatic cancer and is effectively absent in the more advanced disease. This is further borne out by our findings that in patients with poorly differentiated tumors (Gleason score ≥ 7), the citrate ratios (0.085 ± 0.10) were significantly lower ($p < 0.05$) than those (0.398 ± 0.24) among patients with more well-differentiated tumors (Gleason score < 7).

Three-dimensional spectral acquisition using the chemical shift imaging to cover the entire gland for regions of malignancy has been the most recent advance in the field of prostate MRS [3]. This multivoxel acquisition negates the need to know the exact location of the tumor apart from providing the spatial extent, volume and heterogeneity of the tumor. It can be combined with an MRI scan with only 8–17 min of additional scanning time [2]. Metabolic evaluation using MRS may also help in following up these patients after minimally invasive therapies [2].

Conclusions

This study clearly indicates that there is a statistically significant decline in the ratio of citrate to choline plus creatine in the regions of cancer prostate when compared with BPH or normal control. This data can be reliably acquired using a spine coil and may obviate the use of endorectal coils, which cause more discomfort and are more expensive by virtue of being disposable. It may also be possible to prognosticate the disease by evaluating the degree of differentiation based on the citrate ratios. Three-dimensional image analysis in a randomized controlled trial is necessary to help define its role in the management of carcinoma prostate.

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