J Korean Med Sci 1998; 13: 49-53
ISSN 1011-8934

Localized in Vivo Proton Spectroscopy of Renal Cell Carcinoma in Human Kidney

In order to obtain proton magnetic resonance spectra from the renal tumor in human kidney we performed localized magnetic resonance spectroscopy using a saddle-type flexible surface coil. Five patients biopsy-proven as renal cell carcinoma at different stages were put in supine/lateral position to minimize motion artifacts while acquiring the spectrum. Water-suppressed ^{1}H spectra were obtained with localized stimulated echo acquisition mode (STEAM) (20/13.7/2200; TE/TM/TR) and point resolved spectroscopy (PRESS) (288/2200; TE/TR) sequences. The principal resonances in the tumor STEAM spectrum were sorbitol (3.85 ppm), trimethylamines (TMA) (3.25 ppm), two unidentified signals (2.8 and 2.2 ppm), and lipid (0.9-1.8 ppm). In the PRESS spectrum using a long echo time (288 ms), two well localized signals, TMA at 3.25 ppm and lactate at 1.35 ppm were observed from a patient with a tumor at advanced stage. Interestingly only TMA at 3.25 ppm was observed from the patient with a low grade tumor. The spectral patterns of the tumor patients were differrent from those of normal kidney.

Key Words : *Renal cell carcinoma, Lactate, Sorbitol, In vivo ^{1}H MRS*

Duk-Youn Kim, Kap-Byung Kim, Ok-Dong Kim*, Jong-Ki Kim*,**

Departments of Urology, Radiology*, Biomedical Engineering**, School of Medicine, Catholic University of Taegu-Hyosung, Taegu, Korea

Received : August 28, 1997
Accepted : October 28, 1997

Address for correspondence
Jong-Ki Kim, Ph.D.
Departments of Biomedical Engineering and Radiology, Catholic University of Taegu-Hyosung, 3056-6 Taemyung 4-dong, Taegu, Korea
Tel : (053) 650-4335, Fax : (053) 621-4106
E-mail : jkkim@cuth.cataegu.ac.kr

INTRODUCTION

A series of MRS research using animal models (1-4) revealed a number of osmotically active organic solutes, "osmolytes" found in the kidney. These are the polyols sorbitol, inositol, the trimethylamines (TMAs), glycerophosphorylcholine (GPC) and betaine. Two methylamines, GPC and betaine, have been identified in the rat renal medulla (1). More recent work using in vitro spectroscopy assigned two additional metabolites including lactate and myo-inositol from bovine kidney extracts (5). However in the in vivo spectra of normal human kidney all these resonances were not observed except TMA signal. The short T2 and T2* relaxation times of metabolites in tissues other than brain, and artifacts resulting from respiratory and cardiac motion have limited the information obtained from in vivo studies. In spite of efforts to avoid these difficulties including respiratory gating, the spectral resolution obtained was not enough to assign metabolic resonances clearly (5). Designing a surface coil for signal reception and optimized timing parameters of STEAM or PRESS experiments seem to be crucial for detecting the metabolic signals of human kidney with spectral sensitivity and resolution. In vivo spectroscopy in human kidney has endeavored to show variations in the levels of these TMA resulting from dehydration and acute volume loading (5, 6). In addition, in vivo spectroscopy have so far been performed only on normal human kidney (5, 7) or transplanted kidney with normal function (7). Localized phosphorous MRS successfully discriminate renal failure from cyclosporine nephrotoxicity after kidney transplantation (8). It is known that increased levels of sorbitol have been observed in renal failure and diabetes (9). Therefore it is interesting to investigate any metabolic marker for renal disease using localized in vivo proton spectroscopy. We present here a preliminary account of in vivo proton spectroscopy of renal cell carcinoma in human kidney.

METHOD

Localized proton magnetic resonance spectroscopy was performed on five patients with renal mass awaiting

nephrectomy and two healthy volunteers. Biopsy proved these masses as renal cell carcinomas. The pathologic stages of the patients were as follows: patient 1 was T4N0M1 (T4: tumor invades beyond Gerota's fascia. N0: no regional lymph node metastasis. M1: distant metastasis), patient 2 was T2N0M0 (T2: tumor more than 2.5 cm limited to the kideny. N0: no regional lymph node metastasis. M0: no distant metastasis), patient 3 was T3N2M0 (T3: tumor extends into major veins or invades adrenal gland or perinephtic tissues but not beyond Gerota's fascia. N2: metastasis in a single lymph node, greater than 2 cm but no more than 5 cm or multiple nodes none greater than 5 cm. M0: no distant metastasis), patient 4 was T1N0M0 (T1: tumor 2.5 cm or less limited to the kidney. N0: no regional lymph node metastasis. M0: no distant metastasis), and patient 5 T1N0M0. All tumors showed clear cell-type and in patient 1, solid mass included multiple, central necrotic areas, while soft friable tissue was found in patient 2. There was a spherical shaped, partially cystic mass with soft friable tissue in patient 3 and an oval shaped, well demarcated tumor measuring 2×1.5 cm, 2.3×2.2 cm in patient 4 and patient 5.

Patients and volunteers were placed in supine/lateral position to minimize respiratory motion artifacts. All studies were performed using a 1.5 Tesla Signa clinical imager using a flexible surface coil (General Electric Medical System, Milwaukee, USA) to receive and body coil to transmit. The Signa general purpose (GP) flex coil design is a linear, receive-only flexible coil, which consists of two 13 cm×17 cm loops that are serially connected to a corotating "saddle coil" pair, configured to form a Figure 8 coil circuit. This saddle design provides exceptional uniformity across the sensitive volume of the coil and a minimum of bright spot.

The surface coil was tightly secured over the posterior abdominal wall of patients in supine/lateral position to cover the kidney under investigation. Localizer images were obtained on coronal and axial planes with Fast Spoiled Gradient Recalled Echo sequence (Flip angle/TE/TR; 80/14/85) with breath hold. A volume of interest (VOI) (8 cm^3) was chosen graphically from the axial localizer and the offset parameters transferred automatically to the STEAM localization sequence for shimming and spectral acquisition. Water suppression was achieved by preceding chemical-shift selective (CHESS) three orthogonal radiofrequency pulses. Shimming of selected voxel was performed until the water line width was obtained at 6 to 9 hz. Proton spectroscopy was performed with localized STEAM (TE/TM/TR; 20/13.7/2200) and PRESS (TE/TR; 288/2200) sequences. Each spectral acquisition consisted of 2048 complex data points in the time domain with a spectral width of 2,500 hz. Postacquisition processing of the data was restricted to zerofilling to 4 K, mild exponential filtering with line broadening of 1 to 1.5 hz, and phase correction. No further smoothing, resolution enhancement or base line correction was applied.

RESULTS

STEAM spectra from the renal carcinomas of two patients are shown in Fig. 1. Although two patients had the same type of tumor they had different tissue morphology and tumor stage. Lipid signal at 1.5-0.5 ppm and the TMA resonance at 3.2 ppm were observed in both spectra. In the spectrum of patient 2 a significant amount of sorbitol was detected clearly at 3.85 ppm, while a more broad peak shape was observed in the spectrum of advanced tumor patient 1 with solid tissue. In vivo detection of sorbitol resonance has not been reported in human kidney so far. Inositol, observed in bovine kidney, was not detected at 3.6 ppm, whereas it was present with small intensity in the normal kidney spectrum (Fig. 2a). Lipid signal was dominant in the spectrum of patient 1, but it was comparable with other metabolic signals in the spectrum of patient 2. Amino acids resonance around 2.2 ppm was higher than TMA resonance in patient 1, but it was reversed in patient 2. An unidentified signal around 2.8 ppm in the spectrum of patient 1 was not observed in the spectra of patient 2 and normal volunteers.

PRESS spectra using long echo time demonstrated spectral difference even more clearly between five renal cell carcinoma patients as shown in Fig. 1b, Fig. 1b' and Fig. 3. Dominant lipid signals were suppressed or removed in the PRESS spectra, which revealed the presence of lactate signal at 1.35 ppm. Lactate signal, ambiguous due to overlapping with lipid, was clearly resolved in the spectrum of patient 1 (grade III) and patient 3 (grade II) with tumors of relatively advanced stage while it was not observed in the spectra of patients 2, 4, 5 with low stage (Table 1). TMA resonance was detected clearly at 3.2 ppm in the spectra of patients 1, 2, 3, while not observed in the spectra of patients 4, 5 (Fig. 3).

Table 1. Characteristics of the patients

Patient	Age/Sex	Cell type	Grade (Fuhrman)	Pathologic stage
1. Ha SD	61/M	clear cell	grade III	T4N1M1
2. Kang SJ	31/F	clear cell	grade I	T2N0M0
3. Bae CS	67/M	clear cell	grade II	T3N2M0
4. Park KY	36/M	clear cell	grade I	T1N0M0
5. Park MS	62/M	clear cell	grade II	T1N0M0

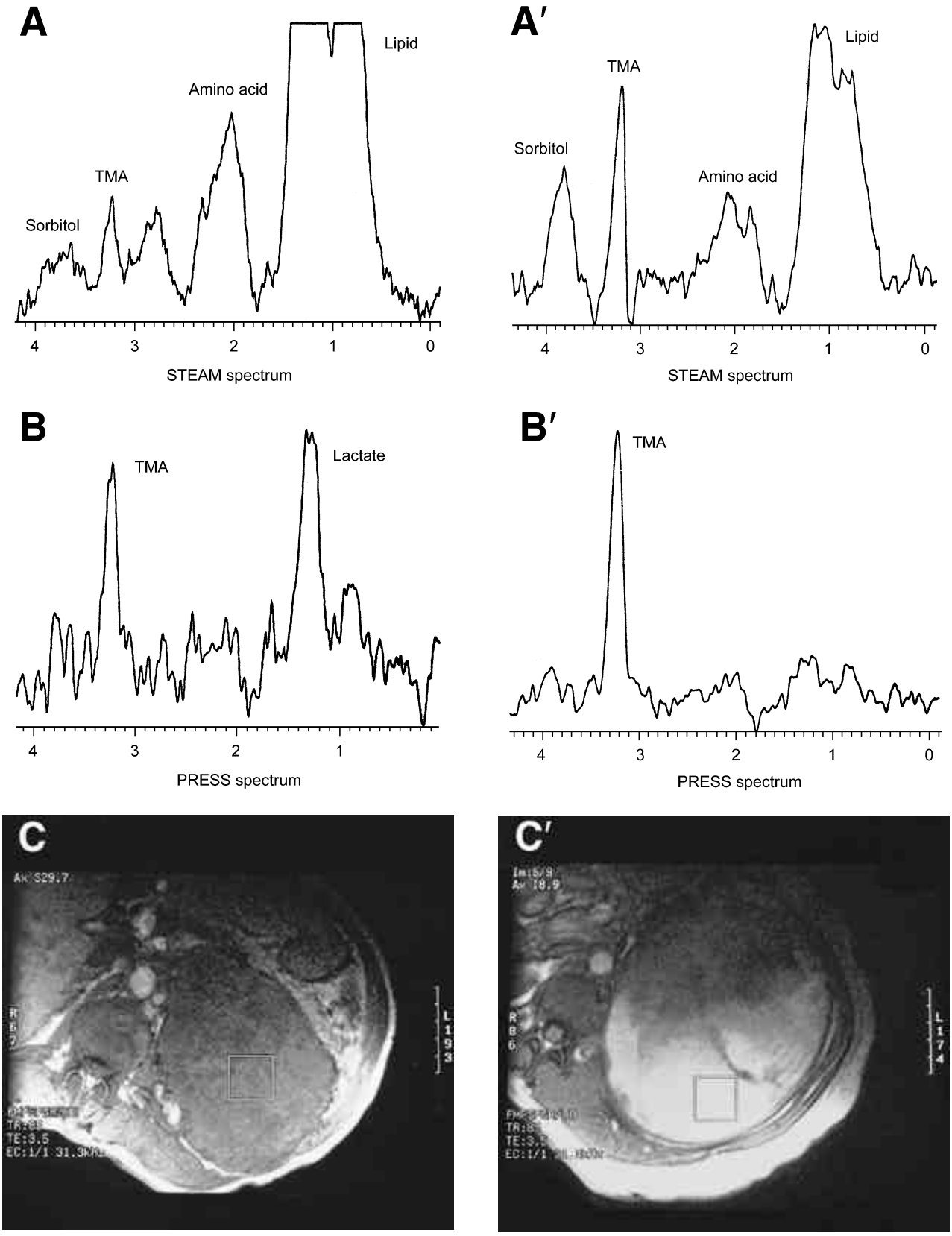

Fig. 1. Water-suppressed STEAM spectrum (A), PRESS spectrum (B), and axial SPGR image and spectroscopy voxel (C) selected from patient 1 with renal cell carcinoma of grade III, and corresponding STEAM (A'), PRESS (B'), and localizer image and voxel (C') of patient 2 with renal cell carcinoma of grade I.

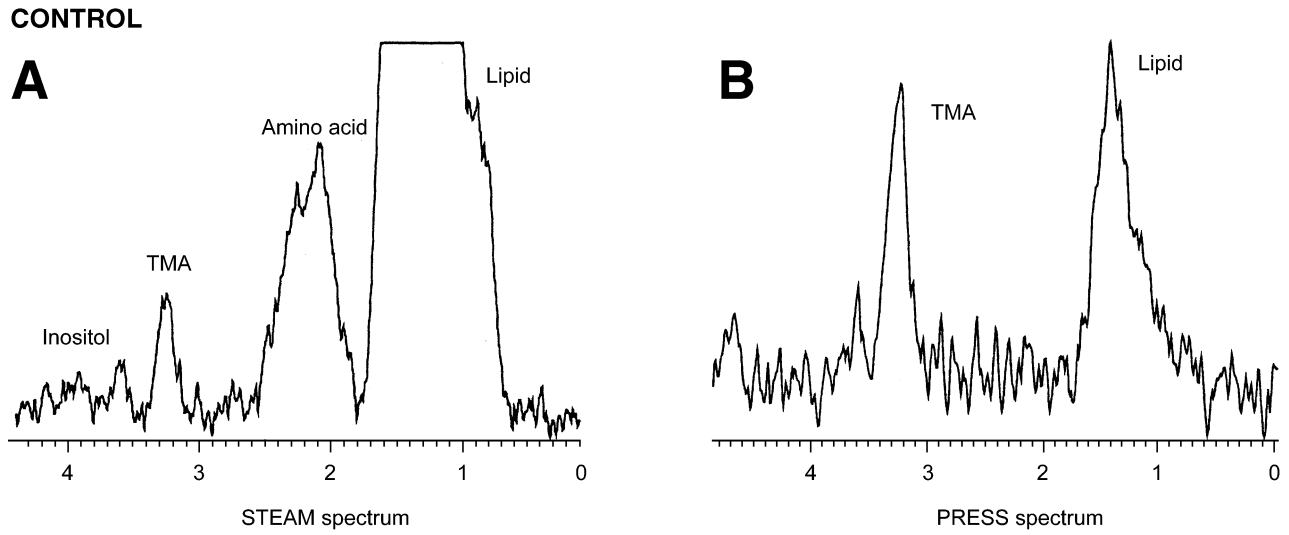

Fig. 2. Water-suppressed STEAM spectrum (A) and PRESS spectrum (B) of normal kidney.

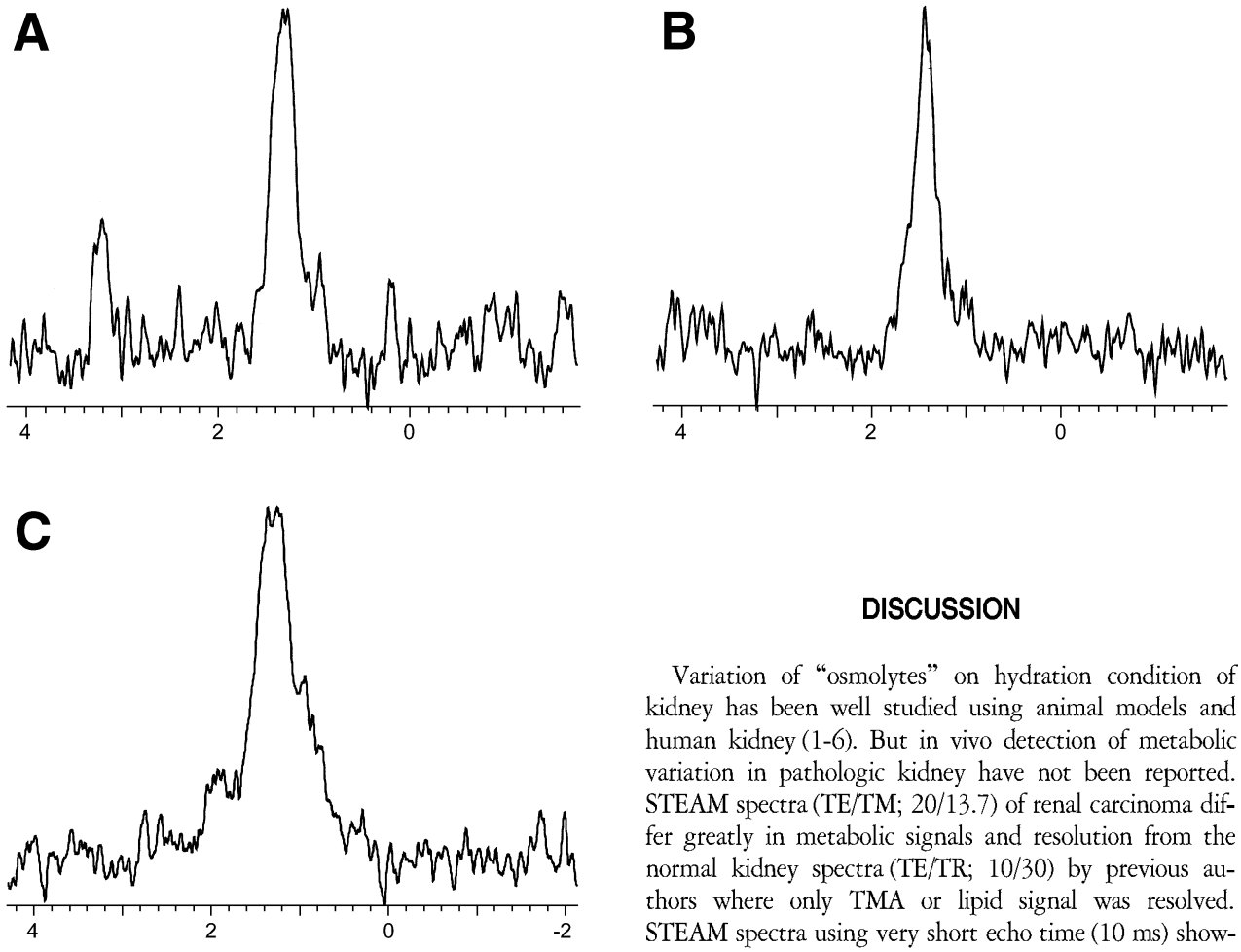

Fig. 3. PRESS spectra of Patient 3 (A), Patient 4 (B), Patient 5 (C), in which TMA resonance at 3.2 ppm was varied over the patients. In Patient 3 (grade II) lactate was observed at 1.3 ppm, and TMA was detected at 3.2 ppm.

DISCUSSION

Variation of "osmolytes" on hydration condition of kidney has been well studied using animal models and human kidney (1-6). But in vivo detection of metabolic variation in pathologic kidney have not been reported. STEAM spectra (TE/TM; 20/13.7) of renal carcinoma differ greatly in metabolic signals and resolution from the normal kidney spectra (TE/TR; 10/30) by previous authors where only TMA or lipid signal was resolved. STEAM spectra using very short echo time (10 ms) showed broad background resonance and prominent lipid signal. Using a longer echo time, such as 20 ms, produced much better spectral resolution compared with previous kidney spectra. Detecting sorbitol particularly in

high grade tumor patient is noteworthy in the sense that the high levels are thought to be associated with abnormal renal function. This observation seems to be the first report of detection of sorbitol in vivo in pathologic kidney as far as we know. Although sorbitol has been observed in the kidney of renal failure or diabetes, in vivo spectroscopy detection has not been reported. The STEAM experiments (TE/TM; 30/13.1) of diabetic kidney with different stages did not obtain the sorbitol signal (unpublished results in our laboratory). But sorbitol was not observed in STEAM spectra of other patients.

A long echo time in PRESS experiment is used to eliminate signal contamination from lipid of short T2 relaxation time. PRESS spectra with a TE of 288 ms revealed a lactate signal at 1.3 ppm in the spectra of patient 1 and patient 3 which was ambiguous due to overlapping with lipid in the STEAM spectrum. This lactate was not observed in the spectra of patients with relatively lower grade. Presence of lactate in patient 1 and patient 3 was well correlated with histologic findings of multiple necrotic areas in tissue morphology. However, in patient 2, although the tumor was graded as II, lactate was not observed. This may reflect differential morphological states of tumor. In the case of patient 5 it appeared that lactate was overlapped with lipid signals. Observation of lactate and choline-containing signal from the tumor tissue is parallel with the proton spectrum of brain tumor or breast tumor. Presence or elevation of choline signal in tumor tissue is a more general finding as reported in various neoplastic tissues in previous works. It is not clear whether apparent doublet signals in the PRESS spectrum of patient 1 are due to intrinsic J-coupling or motional artifacts. In our measurements we found that respiratory gating was not critical for pathologic kidney; the resolution of our spectra is comparable or better than those of published spectra. (5) One published spectrum of normal human kidney using respiratory gating showed broad background in the region of osmolytes resonance. These presumably come from the contribution of macromolecules since they used a very short echo time such as 10 ms in STEAM experiments. In this study using a TE of 20 ms, such background was not observed. Some lipid resonance with relatively long T2 were consistently observed in the long echo time PRESS spectra (Fig. 2b) or STEAM spectra (7) of normal kidney and renal cell carcinoma. But these resonances were absent in the PRESS spectra of two patients (P1 and P2) with renal cell carcinoma. TMA resonance was varied over the patients. It was strong in the PRESS spectra of patient 1, 2 while it was relatively small compared with lipid resonance in patient 3. However, it was absent in the spectra of patients 4, 5, which indicated no correlation with tumor staging. Presently it is not clear whether detecting TMA depends on the hydration condition of patient's renal parenchyma or other pathology. Further study is necessary to ellucidiate its significance for in vivo diagnosing the tumor pathology of renal cell carcinoma.

CONCLUSION

Lactic acid and sorbitol were detected only in advanced renal cell carcinoma using long echo-time PRESS technique and short echo-time STEAM technique, respectively. The metabolic variation observed among renal cell carcinoma and normal kidney demonstrates a potential for proton spectroscopy for tumor staging and monitoring of renal failure.

Acknowledgements

We greatly appreciate the assistance in handling patients given by Mr. Cho Kwang-Ho.

REFERENCES

1. Jue T, Rothman DL, Lohman JA, Hughes EW, Hanstock CC, Shulamn RG. *Surface coil localization of 31P NMR signals from orthotopic human kidney and liver. Proc Natl Acad Sci 1988; 85: 971-4.*
2. Bagnasco S, Balaban R, Fales HM, Yang YM, Burg M. *Predominant osmotically active organic solutes in rat and rat renal medullas. J Biol Chem 1986; 5: 5872-7.*
3. Gullans Sr, Blumenfeld JD, Balschi JA, Kaleta M, B, Brenner RM, Heilig CW, Hebert SC. *Accumulation of major organic osmolytes in rat renal inner medulla in dehydration. Am J Physiol 1988; 255: 626-34.*
4. Wirthensohn G, Beck FX, Guder WG. *Role and regulation of gylcerophosphorycholine in rat papilla. Pelugers Arch 1987; 409: 411-5.*
5. Dixon RM, Frahm J. *Localized proton MR spectrosopy of the human kidney in vivo by means of short time STEAM sequences. Magn Reson Med 1994; 31: 482-7.*
6. Avison MJ, Rothman DL, Nixon TW, Long WS, Siegel NJ. *1H NMR study of renal trimethylamine responses to dehydration and acute volume loading in man. Proc Natil Acad Sci 1991; 88: 6053-7.*
7. Shah NJ, Carpenter TA, Wilkinson ID, Hall LD, Dixon AK, Freer CE, et al. *Localized in vivo proton spectroscopy of the human kidney. Magn reson Med 1991; 20: 292-8.*
8. Grist TM, Charles HC, Sostman HD. *1990 ARRS Executive Council Award. renal transplantation rejection: diagnosis with 31P MR spectrosocpy. 1991; 156: 105-12.*
9. Balaban RS, Burg MB. *Osmotically active organic solutes in the renal inner medulla. Kidney Int. 1987; 31: 562-4.*