Possible Decrease in Free Cholesterol and Fatty Acids Unsaturation in Renal Cell Carcinoma Demonstrated by Breath Hold 1H-MRS

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Introduction

Non-invasive characterization of renal tissue has important implications for the diagnosis of renal malignancies and treatment monitoring. Proton magnetic resonance spectroscopy (^{1}H-MRS) has been shown to aid in tissue characterization using metabolic markers of malignancy (*1-4*). The purpose of the current study was to investigate whether there are metabolic differences between healthy renal tissue and renal cell carcinoma (RCC) that could be observed in vivo by ^{1}H-MRS. A multiple breath hold strategy was used for the ^{1}H-MRS acquisition because this method has been shown to markedly decrease the adverse effects of respiratory motion such as out-of-voxel contamination and phase and frequency variations, and improve the spectral resolution and detection of small signals (*5*).

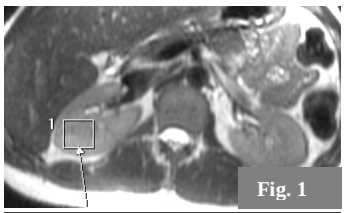

Fig. 1

Materials and Methods

End expiratory breath-hold ^{1}H-MRS data were acquired in the kidneys of 10 healthy volunteers (5 males, 5 females, mean age 25 years, after 4 hours of fasting) and in RCC metastases of 14 RCC patients. Informed consent was obtained in accordance with the guidelines of the institutional review boards of the Massachusetts General Hospital, Dana-Farber Cancer Institute, and Beth Israel Deaconess Medical Center.

The studies were performed on a 3T scanner (Signa LX, General Electric, Waukesha, WI) equipped with a body coil (transmit) and a torso phased array surface coil (receive)(Gore, Newark, DE). Frame-by-frame single voxel (2 x 2 x 2 cm^3) PRESS acquisitions were performed with an echo time of 144 msec, repetition time of 2000 msec, spectral width of 5000 Hz, and 512 points. Each breath-hold (20 sec) included 2 dummy scans and 8 acquisition frames. Eight sets of single breath-holds were typically acquired per voxel. For the healthy kidneys, the MRS voxel was positioned in the axial plane at the level of the hilum of each kidney, to maximize renal tissue within the sample voxel. For the tumors, the MRS voxel was positioned at the center of the tumor.

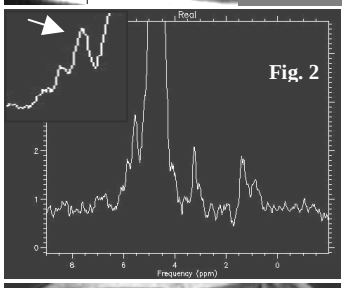

Fig. 2

Spectral processing was performed using SAGE (GE Medical Systems). The FID's were phase-corrected frame-by-frame, zero-filled to 2048 points, and Fourier transformed. The 8 breath-hold datasets were summed in order to maximize the signal-to-noise ratio (SNR). The SNR was standardized to 8 breath holds (64 scans, 2.1 min) and 6.4 cm distance from the nearest surface coil (of the phased array coil).

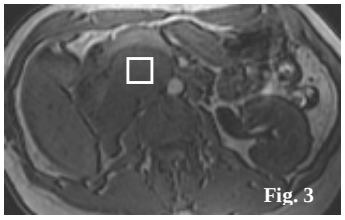
Fig. 3

Results

Fig. 1 demonstrates an axial single shot fast spin echo image of the abdomen of one of the volunteers. The location of the MRS voxel in the kidney is outlined by a white square. The average distance of the MRS voxels in the kidneys to the nearest surface coil was 6.4 ± 0.9 cm (n = 20). **Fig. 2** shows a typical breath hold spectrum of the healthy kidney (voxel shown in Fig. 1). The main resonances are at 5.4 to 5.6 ppm (C6 of cholesterol and the unsaturated parts of the olefinic region of fatty acids (FA)), 4.7 ppm (residual water signal), 3.2 ppm (trimethylamine moiety of choline metabolites), 1.3 ppm (methylenes of FA, triglycerides (TG), and phospholipids (PL)), and ~0.9 ppm (terminal methyls of FA, TG, and PL, and cholesterol methyls). Signals at 2.1 to 2.2 ppm and at 2.5 to 2.6 ppm, attributed to methylenes of cholesterol and FA as well as amino acids, were occasionally detected. Inset: expansion of the chemical shift range showing the resonance at 5.4 ppm (arrow).**Fig. 3** demonstrates an axial image of the abdomen of one of the patients. The location of the MRS voxel in the center of the tumor is outlined by a white square. **Fig. 4** shows the breath hold spectrum of the tumor that is shown in Fig. 3. Note the presence of prominent resonances at 3.2 and 1.3 ppm and the absence of the resonance at 5.4 ppm. The mean SNR of the resonances in the healthy kidneys and the tumors is summarized in Table 1.

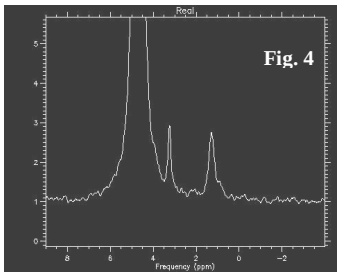

Fig. 4

Table 1. SNR of ^{1}H-MRS resonances in healthy kidney and RCC metastases.

	5.4 ppm	3.2 ppm	1.3 ppm	SNR 5.4 ppm / SNR 1.3 ppm
Healthy Kidney (10 volunteers)	7.3 ± 7.4	6.8 ± 2.1	30.9 ± 31.7	0.425 ± 0.406*
RCC metastases (14 patients)	4.3 ± 14.7 **	6.6 ± 8.1	43.1 ± 79.1	0.022 ± 0.056

The data are given as mean ± standard deviation. In the healthy kidneys the resonances appeared in all the spectra (n = 10). The data of the right kidney of each volunteer are reported. *Statistically significant difference between healthy kidneys to RCC metastases, P=0.0041 on a two-tail t-test. ** Detected in 2 of the 14 spectra.

Discussion and Conclusions

Excised human renal tissues show more esterified cholesterol and less free cholesterol in renal cell carcinoma (RCC) compared to healthy kidney tissue and a decrease in the total unsaturation of the olefinic part of FA was also found in renal neoplastic tissues (*6*). As the resonance at 5.4 ppm is due to cholesterol (specifically in micelles (*7*)) and to the saturated olefinic regions of FA, its absence from the in vivo spectra of RCC metastasis may be in agreement with the ex-vivo findings. Although the resonance at 5.4 ppm is due to both esterified cholesterol and free cholesterol, the esterified form of cholesterol in RCC was found to be bound to oleate which might limit its detection in vivo. Therefore, a decrease in unsaturation of FAs and a shift from free cholesterol to bound cholesterol may be the biochemical basis that underlies the absence of the signal at 5.4 ppm in RCC spectra. Because both inclusion of more lipids in the voxel and out-of-voxel lipid contamination may result in an increase in the concentration of the unsaturated olefinic region and therefore an increase in the signal at 5.4 ppm that is not relevant to the underlying biochemical alterations of the malignant tissues, we calculated the SNR ratio of the 5.4 ppm signal to that of the 1.3 signal (whereas the latter may be correlated to lipid content in the voxel). This ratio was significantly lower in the RCC metastasis, suggesting that this ratio may be a useful marker for renal malignancy and may potentially aid in monitoring treatment.

Previously, the presence of the signal at 3.2 ppm (attributed to choline metabolites) was found to be a marker of malignancy in the breast (*2*). However, here the level of this signal was found to be similar in malignant and healthy renal tissue. However, choline metabolism is tissue specific (*8*). The kidney has an important role in ridding the body of excess circulating choline to prevent cholinergic intoxication and choline metabolites are osmolytes that are important for kidney function. The results of this study further demonstrate the importance of interpreting pathological metabolic findings in the context of the healthy tissue.

References

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