^{1}H MRS of Pancreatic Juice: An MRS-based Diagnostic Approach for the Detection of Pancreatic Cancer

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INTRODUCTION: Pancreatic cancer is the fourth most common cause of cancer-related deaths with a very low overall 5-year survival rate (<5%) which has not improved for the last 25 years [1]. Pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs) are pre-neoplastic lesions having malignant potential. Early diagnosis of pancreatic cancer will increase patients' survival rate. Proteomic analysis of pancreatic juice has been considered to be promising in the early diagnosis of pancreatic cancer. Such studies have detected molecular alterations (K-ras mutations, telomerase reactivation, or methylation of the tumor-suppressor genes) in pancreatic juice samples obtained from patients with pancreatic cancer [2]. However, no definitive molecular markers have been identified yet for the early diagnosis of pancreatic cancer. In this study, we have performed ^{1}H-MRS-based biochemical analysis of pancreatic juice samples from patients with pancreatitis, pancreatic cancer, and precursor lesions such as IPMNs, and MCNs.

MATERIALS & METHODS: Pancreatic juice samples (n=17) were obtained from patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) examination for various pancreatic diseases (Chronic pancreatitis=5; unclear cystic lesions=7; IPMNs=2; adenocarcinoma=1; other benign pancreatic diseases=2). 1D ^{1}H MR spectra were obtained using one-pulse and CPMG sequences with water presaturation and 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt (TSP) was used as an external reference (0 ppm). Experiments were performed on a 600 MHz Avance spectrometer (Bruker Biospin, Canada) using a BBI probe equipped with z-gradient. 2D ^{1}H-^{1}H COSY, TOCSY and ^{1}H-^{13}C HSQC experiments were also performed to support biochemical characterization. The following acquisition parameters were used: number of scans = 64, 90^0 pulse = 7.9 µs, number of points in the time domain = 32 k, spectral width = 7211 Hz, acquisition time = 2.27 s and line broadening for exponential window function = 0.3 Hz. In the CPMG experiments similar parameters were used along with an effective echo-time of 480 ms (τ = 600 µs and loop for T_2 filter = 400).

RESULTS & DISCUSSION: Figure 1 shows typical ^{1}H MR spectra (CPMG) of pancreatic juice samples from patients with chronic pancreatitis, pancreatic cancer, IPMNs and cystic lesions showing their spectral patterns. Various biochemicals in pancreatic juice samples were identified by combined analysis of 1D and 2D MRS experiments. The analysis revealed the presence of various amino acids – branched chain amino acids (valine, leucine, and isoleucine), alanine, threonine, glutamine, lysine, tyrosine, histidine, phenylalanine, tryptophan and other small molecules such as lactate, acetate, formate, urea, and glucose (Figure 1).

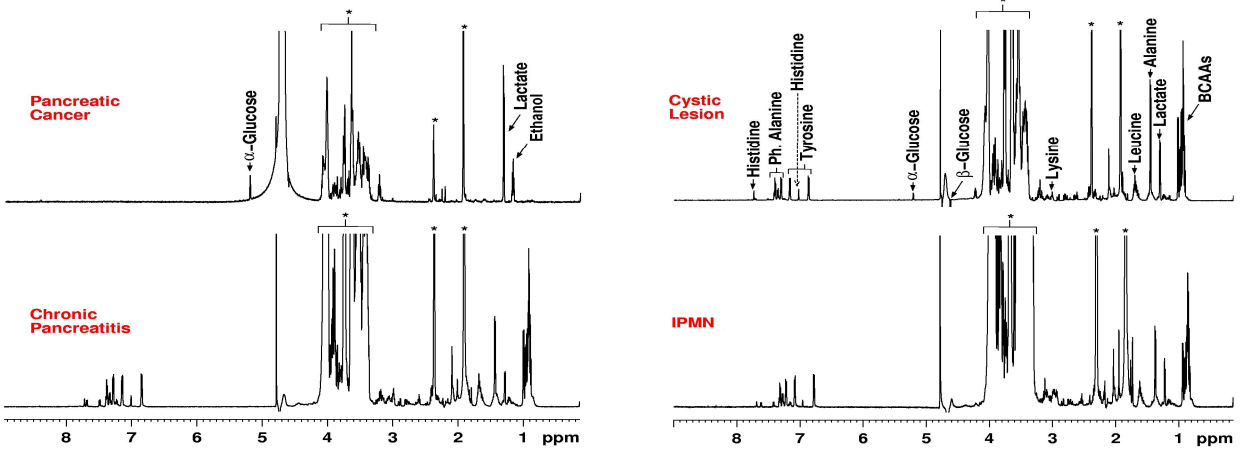

Figure 1: Typical ^{1}H MR spectra (CPMG) of pancreatic juice samples from patients with chronic pancreatitis, pancreatic cancer, IPMN and cystic lesion showing their spectral patterns (*: Contrast agent (Omnipaque); BCAAs: branched chain amino acids).

From Fig. 1, it is clear that the spectral patterns of chronic pancreatitis, cystic lesions and IPMNs are found to be similar whereas the spectrum from pancreatic cancer (adenocarcinoma) patient shows a different pattern. This spectrum is characterized by the absence/decreased levels of the common metabolites present in pancreatic juice except for lactate and glucose which are elevated in the cancer patient compared to the benign patients. The presence of elevated levels of lactate could be attributed to the anaerobic glycolysis in the hypoxic tumor microenvironment [3], whereas the elevation in the levels of glucose could be associated with the diabetic state of pancreatic cancer patients and the marked insulin resistance [4]. In cancer biology, one would expect decreased levels of glucose and elevated levels of lactate, but due to the apparent insulin resistance in pancreatic cancer patients, glucose is not cleared from the body which may contribute to its presence at elevated levels in pancreatic juice of these patients. Magnetic resonance spectroscopy of pancreatic juice could be valuable in detecting pancreatic cancer and differentiating it from other non-malignant pancreatic abnormalities. However, this preliminary study did not differentiate among the spectral patterns of chronic pancreatitis, IPMNs, and cystic lesions. Progression of precursor lesions into invasive adenocarcinoma could be considered as a multistep phenomenon, and a comprehensive analysis of pancreatic juice samples from patients with precursor lesions using metabolomics approach could be valuable in the early detection of pancreatic cancer. A large patient cohort is required for that purpose and patient recruitment towards that goal is underway.

CONCLUSION: ^{1}H MRS of pancreatic juice can differentiate spectral patterns of pancreatic cancer from those of benign pancreatic diseases. Some benign lesions may have malignant potential, and a detailed spectral analysis using chemometric tools will be of help in assessing that.

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