

RAPID COMMUNICATION

Diffusion-Weighted MR Imaging in the Evaluation of Pancreatic Exocrine Function Before and After Secretin Stimulation

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OBJECTIVES: To evaluate diffusion weighted MR imaging before and after secretin stimulation in the assessment of pancreatic exocrine function in the setting of chronic pancreatitis.

METHODS: Nine patients with severe chronic pancreatitis and sixteen patients without chronic pancreatitis but with a history of chronic alcohol consumption were enrolled in the chronic pancreatitis and risk groups, respectively. Thirty-eight patients without any pancreatic disease or history of alcohol consumption were included in the control group. Diffusion weighted images were obtained before and after secretin administration in all patients. The peak ADC values and times were determined and intergroup differences were compared. A receiver operating characteristic curve (ROC) was used to identify the cutoff values of the peak ADC times for discrimination of control group from risk and chronic pancreatitis groups.

RESULTS: In the control group, a peak increase in ADC value of 57–120% (median: 75%) was observed between 90 s and 4 min (median: 2 min) after administration of secretin (Pattern 1). In the risk group, in 13 patients, a peak increase of 52–150% was observed between 4 and 8 min (median: 7 min; Pattern 2). Peak times were significantly longer in risk group ($p < 0.01$). In three patients in the risk group, and in all patients in the chronic pancreatitis group, no ADC peak was observed within 10 min following secretin administration (Pattern 3). Using a peak time of 4 min as the cut-off value, a sensitivity of 100% and specificity of 94.7% were achieved in discriminating the control group from the combined risk and chronic pancreatitis groups.

CONCLUSION: Diffusion-weighted MR imaging before and after secretin administration could yield clinically useful information for detecting pathophysiologic alterations in the setting of chronic pancreatitis.

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INTRODUCTION

Chronic pancreatitis is an inflammatory disease characterized by irreversible damage to pancreatic structure and function. In the majority of cases the pathology is related to chronic alcohol consumption. The severity of chronic pancreatitis has been classified according to the morphologic changes of the pancreatic ducts, as defined in the 1983 Cambridge Symposium (1). The diagnosis of chronic pancreatitis at an early stage is a clinical challenge. Currently available imaging modalities have limited sensitivity or specificity for diagnosing early chronic pancreatitis. Furthermore, pancreas is generally not biopsied to make a diagnosis of this entity because of high complication rate of the procedure (2).

Diffusion-weighted MR imaging is based on intravoxel incoherent motion imaging that allows visualization of molecular diffusion and microcirculation of the blood in the capillary network (perfusion) of biologic tissues (3, 4). The diffusion-

weighted MR images are quantified by an apparent diffusion coefficient (ADC), which integrates both diffusion and perfusion (5). The ADC is equal to the true diffusion coefficient D when diffusion is the only type of motion present. In *in vivo* tissues, however, the reported ADCs have often higher values than expected because of the effect of perfusion (5).

Secretin is a hormone which acts chiefly on the pancreatic duct cells to cause an outpouring of pancreatic juice. In response to secretin, the pancreas produces a large volume of watery fluid rich in bicarbonate content. Secretin stimulation also causes an increase in pancreatic blood flow. The increased mobility of water molecules and increased circulation in the capillaries of pancreas might be quantified through diffusion-weighted MR imaging. In general, increases in diffusion and perfusion cause decrease in signal intensity on diffusion weighted MR images and increases in ADC values (3). In the present study, our aim was to evaluate diffusion-weighted MR imaging before and after secretin stimulation

for the assessment of pancreatic exocrine function in the setting of chronic pancreatitis.

METHODS

Nine patients (five men, four women) aged 60–76 years (mean age: 67.8 years) with severe chronic pancreatitis, as defined by the Cambridge criteria constituted the chronic pancreatitis group. Sixteen patients (12 men, 4 women) aged 57–78 years (mean age: 67.3 years) without chronic pancreatitis and with a history of alcohol intake more than 50 g/day for at least 7 yr (mean: 8.8 yr; range: 7–12 yr) were enrolled in the risk group. Finally, 38 patients (10 men, 28 women) aged 59–74 yr (mean age: 65.3 yr) without pancreatic disease were included in the control group; the control group comprised of patients who had undergone routine MR imaging for evaluation of biliary ducts, they had no pancreatic symptoms, pathologies or history of alcohol consumption. Our institutional review board has approved this study and informed consent was taken from all enrolled subjects.

All study subjects underwent DW-MRI using a 1.5 T MR unit using a dedicated receive only body coil (GE Healthcare, Milwaukee, WI), before and after IV administration of 1 clinical unit per kilogram body weight secretin (Secrepan; Eisei, Tokyo, Japan). Diffusion weighted images (single-shot SE-EPI; TR = ∞ , TE = 80 ms, ETL = 128) were obtained with diffusion weightings of $b = 0$ s/mm² and $b = 400$ s/mm² before and every 30 s after the secretin administration in the first 2 min and every minute in the next 8 min. A circular region of interest (ROI) was drawn in the pancreatic parenchyma on diffusion weighted MR images with diffusion weighting $b = 0$ s/mm² while avoiding positioning ROI on the main pancreatic duct; the ROI was then copied to the corresponding ADC maps, and an ADC-time curve was created.

One-way analysis of variance was used to investigate intergroup differences in patient age. Gender distribution was compared across groups with the χ^2 test. The peak ADC

values and times of patients were determined using ADC-time curves, and intergroup differences were compared using Mann-Whitney U test. The alteration patterns observed in ADC values were attempted to classify. A receiver operating characteristic curve (ROC) was used to identify the cutoff values of the peak ADC times; controls were considered negative, and patients in the risk and chronic pancreatitis groups were considered positive. Sensitivity and specificity of the technique were calculated with 95% confidence intervals.

RESULTS

There were no significant intergroup differences regarding the patient age and gender distribution. In the control, risk, and chronic pancreatitis groups, the median baseline ADC values were 1.2×10^{-3} mm² (range: 1×10^{-3} mm²– 1.7×10^{-3} mm²), 1.2×10^{-3} mm² (range: 0.6×10^{-3} mm²– 2.1×10^{-3} mm²), and 1.1×10^{-3} mm² (range: 0.8×10^{-3} mm²– 1.2×10^{-3} mm²), respectively. In the control group, a peak increase in ADC value of 57–120% (median: 75%) was observed between 90 s and 4 min (median: 2 min) after injection of secretin (Pattern 1) (Fig. 1). In the risk group, in 13 patients, a peak increase of 52–150% was observed between 4 and 8 min (median: 7 min). Although there was no significant difference regarding the peak increase rates, peak times were significantly longer in risk group ($p < 0.01$; Pattern 2). In three patients, in the risk group, no ADC peak was observed within 10 min following secretin injection; the ADC values showed fluctuations of 10% around the baseline (Pattern 3). Likewise, in the chronic pancreatitis group, we were not able to detect any ADC-peak, but only fluctuations of $\pm 10\%$ around the baseline in all patients (Pattern 3). To perform ROC analysis, patients without ADC peaks were treated as having peak time at 10 min since this was the maximum possible time in our study. The area under the curve was 0.998 (95% CI = 0.992–1) (Fig. 2). The cut-off point derived from the curve was 4 min. The sensitivity and specificity of

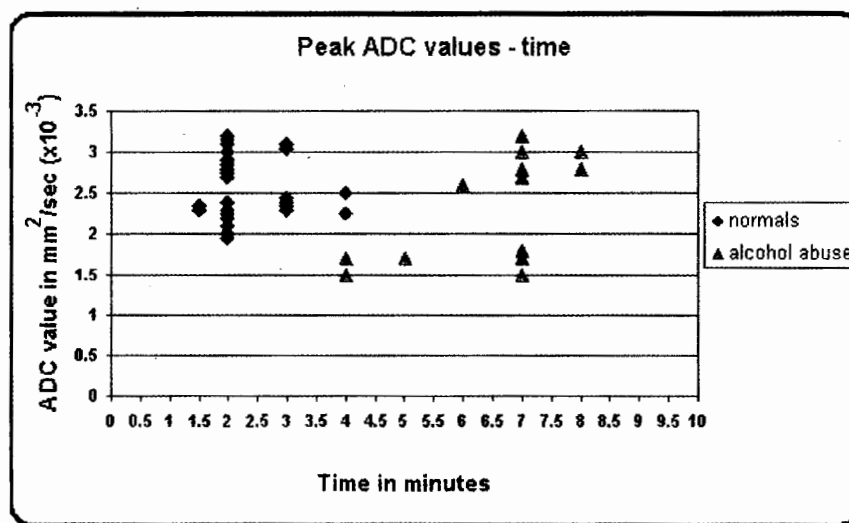


Figure 1. Scatter diagram showing peak ADC times (x-axis), and values (y-axis) in controls and subjects with chronic alcohol consumption.

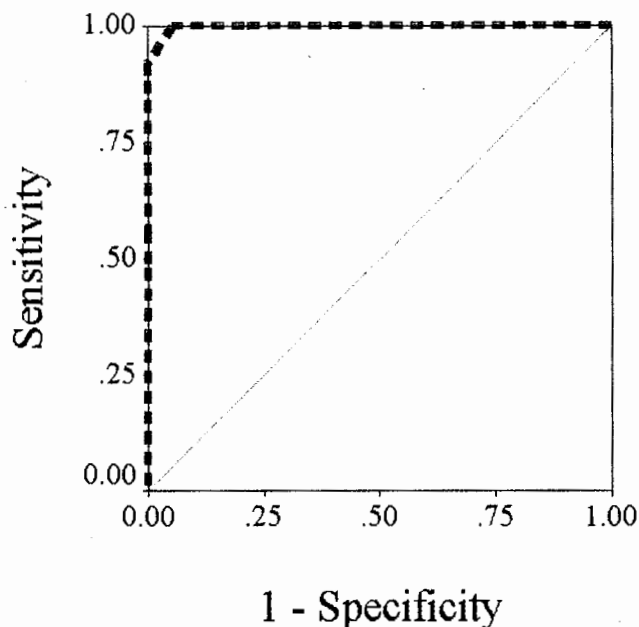


Figure 2. Receiver operating characteristics curve (ROC) of correlation between sensitivity and false-positive rate (1-specificity) for ADC peak time.

the test at this level was 100% (95% CI = 83.4%–100%) and 94.7% (95% CI = 80.9%–99.1%), respectively.

DISCUSSION

Although the invasive secretin test is considered the gold standard for testing exocrine pancreatic insufficiency, it is performed by very few centers around the world (1). Since histological findings are not usually available, the diagnosis of chronic pancreatitis in almost all centers rests on imaging studies. Endoscopic retrograde cholangiopancreatography (ERCP) and its counterpart magnetic resonance cholangiopancreatography (MRCP) are considered as important tools in the evaluation of chronic pancreatitis (2). However, it is well known that chronic pancreatitis can exist in the presence of a normal pancreatogram. It is suggested therefore that imaging procedures and pancreatic function testing complement each other. Fecal elastase-1 and fecal chymotrypsin tests are the noninvasive function tests with a sensitivity of 38–87%, and 21–49% for mild to moderate chronic pancreatitis, respectively (1). However, just like the invasive secretin test, the fecal tests do not allow a dynamic investigation of pancreatic exocrine function either. In these tests, measured pancreatic exocrine outcome is the cumulative amount of a particular indicator, such as bicarbonate output or enzyme levels, throughout a particular time period. Therefore, it is not possible to detect any differences in the early time period following the stimulation of exocrine pancreas with secretin.

In response to secretin, carbon dioxide diffuses to the interior of the pancreatic ductal cell from the blood and combines with water to form carbonic acid. The carbonic acid in turn dissociates into bicarbonate ions and hydrogen ions. Then the bicarbonate ions are actively transported in association

with sodium ions into the lumen of the duct. The movement of sodium and bicarbonate ions from the blood into the duct lumen creates an osmotic gradient that causes osmosis of water also in the pancreatic duct (7). In the present study, we hypothesized that diffusion-weighted MR imaging can be employed to detect this movement of water molecules; an increase in movement of water molecules should express itself in signal losses on diffusion-weighted MR images and hence increased ADC values.

Chronic alcohol consumption is considered as the major cause of chronic pancreatitis (8–10). Assuming that patients with chronic alcohol consumption are under great risk for developing the disease, it might be hypothesized that some impairment in the pancreatic function would occur before the development of irreversible changes of the chronic pancreatitis. Thus, this group might be considered a model for investigating early pathophysiologic alterations in chronic pancreatitis.

Using a dynamic technique and ADC-measurements, we were able to show differences in the response patterns of the control, risk, and chronic pancreatitis groups to secretin stimulation. In the control group, an early peak occurred within the first 4 min after the injection of secretin; in the risk group, we were able to detect a delayed peak with comparable amplitude to that in the control group between 4 and 8 min after the secretin injection. In three patients in the risk group, and in all patients in the chronic pancreatitis group, a peak was not detectable within the first 10 min after the secretin injection. Using 4 min as the cut-off value, we achieved a sensitivity of 100% and specificity of 94.7% in discriminating the control group from the combined risk and chronic pancreatitis groups.

In their animal study, Arai *et al.* compared pancreatic exocrine secretion in WBN/Kob rats, a model of chronic pancreatitis, with that in Wistar rats of the same age (11). When secretin was intravenously administered, pancreatic secretion was stimulated in Wistar rats, but the stimulation of fluid secretion was much weaker in WBN/Kob rats (11). This reduced reaction can be induced by a decrease in secretin binding to its receptors on the membrane of pancreatic ductal cells. In our study, this decrease was expressed in delayed ADC peaks in chronic alcohol consumers, and absent peaks in chronic pancreatitis patients.

The ADC is an artificial parameter, without any intrinsic physical relevance, that combines diffusion and perfusion (5). The baseline ADC values in our study were as expected and in concordance with a previous study of Yamada *et al.* They stated that regarding ADC values, the diffusion part is approximately 70% and the perfusion fraction is approximately 30% (without secretin stimulation) in the pancreas. In diffusion-weighted MR imaging, the b-value has units of seconds per square millimeter and represents the overall sensitivity of the MR sequence to motion. In general, with b-values greater than 300 s/mm², the resultant ADC value contains negligible amounts of perfusion factor. With b-values greater than 1,000 s/mm², an ADC value would probably more closely approximate the true diffusion coefficient D (5). In the present study,

we employed a b-value of 400 s/mm². Thus, the ADC values we obtained probably had a small perfusion fraction as well. Experimental work has shown a link between secretin stimulation and increased glandular blood flow (12, 13). It has been reported that alcoholic chronic pancreatitis is associated with tissue fibrosis and reduction of blood vessel density on histologic examination (14). Flow measurement studies have shown decreased blood flow in patients with chronic pancreatitis (15, 16). Schilling *et al.* assessed pancreatic blood flow by laser Doppler flowmetry in 9 patients and 13 normal patients and found that blood flow in the pancreas was significantly decreased in chronic pancreatitis (15). Lewis *et al.* measured pancreatic blood flow using the hydrogen gas technique and an endoscopically placed platinum ductal electrode (16). In their study, whereas the blood flow was increased in healthy controls after IV secretin, there was not such an increase in patients with chronic pancreatitis. This phenomenon might have also played an important role in our study. Increased blood flow, or in other words perfusion, after IV secretin in controls with normal pancreatic exocrine function might have probably contributed to the early peak in ADC values in this group.

Our findings suggest that diffusion-weighted magnetic resonance imaging could yield clinically useful information for detecting pathophysiologic alterations in chronic pancreatitis. For example, a patient with vague abdominal pain and suspect of having chronic pancreatitis might be evaluated using this technique for detecting any impairment in the pancreatic exocrine function. Nevertheless, our approach needs validation and a prospective study of reproducibility to establish its correlation with clinical findings.

STUDY HIGHLIGHTS

- In patients with chronic pancreatitis, the ADC values were significantly lower than those in normal controls.
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REFERENCES

1. Otsuki M. Chronic pancreatitis. The problems of diagnostic criteria. *Pancreatology* 2004;4:28-41.
2. Mitchell RM, Byrne MF, Baillie J. Pancreatitis. *Lancet* 2003;361:1447-55.
3. Sumi M, Takagi Y, Uetani M, et al. Diffusion-weighted echoplanar MR imaging of the salivary glands. *Am J Roentgenol* 2002;178(4):959-65.
4. Le Bihan D, Breton E, Lallemand D, et al. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology* 1988;168(2):497-505.
5. Yamada I, Aung W, Himeno Y, et al. Diffusion coefficients in abdominal organs and hepatic lesions: Evaluation with intravoxel incoherent motion echo-planar MR imaging. *Radiology* 1999;210(3):617-23.
6. Szafer A, Zhong J, Anderson AW, et al. Diffusion-weighted imaging in tissues: Theoretical models. *NMR Biomed* 1995;8:289-96.
7. Guyton AC, Hall JE. *Textbook of Medical Physiology*, 10th Ed. Philadelphia: WB Saunders, 2000.
8. Hamada H, Ishiguro H, Yamamoto A, et al. Dual effects of n-alcohols on fluid secretion from guinea pig pancreatic ducts. *Am J Physiol Cell Physiol* 2005;288(6):C1431-9.
9. Gullo L. Alcohol and chronic pancreatitis: leading or secondary etiopathogenetic role? *JOP* 2005;6(Suppl 1):68-72.
10. Stevens T, Conwell DL, Zuccaro G. Pathogenesis of chronic pancreatitis: An evidence-based review of past theories and recent developments. *Am J Gastroenterol* 2004;99(11):2256-70.
11. Arai I, Komatsu Y, Sasaki K, et al. Reduced reactivity of pancreatic exocrine secretion in response to gastrointestinal hormone in WBN/Kob rats. *J Gastroenterol* 1998;33:247-53.
12. Beijer HJ, Brouwer FA, Charbon GA. Time course and sensitivity of secretin-stimulated pancreatic secretion and blood flow in the anesthetized dog. *Scand J Gastroenterol* 1979;14(3):295-300.
13. Chung RS, Safaie-Shirazi S. The effect of secretin on pancreatic blood flow in the awake and anesthetized dog. *Proc Soc Exp Biol Med* 1983;173(4):620-5.
14. De Angelis C, Valente G, Spaccapietra M, et al. Histological study of alcoholic, nonalcoholic, and obstructive chronic pancreatitis. *Pancreas* 1992;7(2):193-6.
15. Schilling MK, Redaelli C, Reber PU, et al. Microcirculation in chronic alcoholic pancreatitis: A laser Doppler flow study. *Pancreas* 1999;19(1):21-5.
16. Lewis MP, Lo SK, Reber PU, et al. Endoscopic measurement of pancreatic tissue perfusion in patients with chronic pancreatitis and control patients. *Gastrointest Endosc* 2000;51(2):195-9.