

## PANCREAS ALERTS

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*Pancreatology 2005; 5(2-3):201-4.*  
(PMID: 15855816)

### **Plasmapheresis in the management of acute severe hyperlipidemic pancreatitis: Report of 5 cases.**

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Hyperlipidemic pancreatitis is an acute and potentially life-threatening complication of hypertriglyceridemia that can be provoked when triglyceride levels (TGL) exceed 11.3 mmol/L (1,000 mg/dL). Except for standard symptomatic treatment, plasmapheresis has been performed to rapidly reduce TGL and chylomicron levels in the blood. In 5 patients with hyperlipidemic pancreatitis, treatment with plasmapheresis was evaluated. Five male patients who suffered from acute pancreatitis with severe primary hyperlipidemia were studied. In addition to the standard treatment, they were treated with plasmapheresis. Plasma exchange lowered the lipid level and TGLs in all cases. It also improved abdominal pain, the clinical state of the patients, and signs and symptoms of the disease. Complications of treatment were not encountered, none of the patients died and only 1 patient underwent surgery. Follow-up of the patients lasted 4-28 months, and recurrence of pancreatitis was not noted. This study showed that plasmapheresis was successfully applied in patients with hyperlipidemic pancreatitis, especially to improve the acute phase of the disease.

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### **Early sequential changes in serum markers of acute pancreatitis induced by endoscopic retrograde cholangiopancreatography.**

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Trypsinogen activation is thought to play a crucial role in the pathogenesis of acute pancreatitis (AP). Our aim was to characterize the very early sequential changes of trypsinogen-1, trypsinogen-2, the trypsin-2-alpha(1)-antitrypsin complex (T2-AAT), and pancreatic secretory trypsin inhibitor (PSTI) in serum from patients with pancreatitis induced by endoscopic retrograde cholangiopancreatography (ERCP), a model for studying the early phase of the disease in humans. The study population consisted of 659 consecutive patients with 897 ERCP procedures. Blood samples were obtained before and at different time points after the procedure. The serum concentrations of trypsinogen-1 and trypsinogen-2, PSTI and T2-AAT were determined by time-resolved immunofluorometric assays. ERCP-induced pancreatitis developed after 50 of the 897 ERCP procedures (5.6%). Sixty-one randomly selected ERCP patients without post-ERCP pancreatitis served as controls. Trypsinogen-1 and trypsinogen-2 showed an equally steep increase during the two first hours after ERCP in patients developing AP, but trypsinogen-1 decreased more rapidly than trypsinogen-2, which remained elevated during the 5-day study period. Serum PSTI also increased rapidly whereas T2-AAT increased more slowly peaking at 24 h. In patients developing post-ERCP pancreatitis the median concentration of trypsinogen-1 was markedly higher than in the controls

already before the ERCP procedure. In the control group the concentrations of trypsinogen-1, trypsinogen-2, PSTI and T2-AAT did not change significantly. The rapid increase of trypsinogen-1 and trypsinogen-2 and PSTI in the early phase of AP suggests that release of pancreatic enzymes is the initial event while the delayed increase of T2-AAT may reflect that the capacity of the intrapancreatic PSTI-based inhibitory mechanism has been exhausted.

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### **Genetic and biochemical characterization of the E32del polymorphism in human mesotrypsinogen.**

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Mesotrypsin is a minor pancreatic digestive enzyme that degrades dietary trypsin inhibitors in the gut. In this study, the authors tested the hypothesis that the E32del genetic variant of mesotrypsin might represent a risk factor for the development of chronic pancreatitis, as a result of enhanced degradation of pancreatic secretory trypsin inhibitor. The authors screened 97 German patients with chronic pancreatitis of alcoholic etiology and 109 healthy controls for the presence of the E32del variant and characterized the biochemical properties of E32del mesotrypsinogen. Higher allele frequency of the E32del variant was detected in the control population (25.7 vs. 18.0%), but the difference was not significant ( $P=0.062$ ). Recombinant E32del mesotrypsin exhibited normal catalytic activity, characteristic inhibitor resistance and inability to activate pancreatic zymogens. Degradation of trypsin inhibitors was unaffected by the E32del

genotype. Interestingly, mesotrypsinogen-E32del was biochemically distinguishable from mesotrypsinogen by its faster activation with bovine enterokinase, while activation by human enterokinase, trypsin or cathepsin B was unchanged. The results classify E32del mesotrypsinogen as a frequent polymorphic variant, which is not associated with chronic alcoholic pancreatitis.

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### **Histopathologic characteristics of autoimmune pancreatitis based on comparison with chronic pancreatitis.**

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The authors evaluated the histopathologic characteristics of autoimmune pancreatitis (AIP). The study was based on comparison with both chronic alcoholic pancreatitis (CAP) and chronic obstructive pancreatitis (COP). Three AIP patients, 17 CAP patients, and 19 COP patients were studied histopathologically. There was a dense lymphoplasmacytic infiltrate, especially within and around the pancreatic ducts, and fibrosis associated with AIP, while there was fibrosis accompanied by mild inflammatory infiltration in both CAP and COP. Inter- and intralobular fibrosis admixed with acinar atrophy was observed in both AIP and COP, while interlobular fibrosis combined with a "cirrhosis-like" appearance was found in CAP. Obliterative phlebitis was found in AIP, while thrombosis of the splenic vein was exhibited in CAP. Autoimmune pancreatitis was histologically characterized by dense lymphoplasmacytic infiltrate combined with fibrosis, acinar atrophy, obliterative phlebitis, and ductal involvement.

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**Immune responses to DNA mismatch repair enzymes hMSH2 and hPMS1 in patients with pancreatic cancer, dermatomyositis and polymyositis.**

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To identify tumor antigens useful for diagnosis and immunotherapy of patients with pancreatic ductal adenocarcinoma, the authors applied a SEREX approach with a cDNA library made from 5 pancreatic cancer cell lines and sera obtained from 8 patients with pancreatic cancer, and isolated total 32 genes, including 14 previously characterized genes and 18 genes with unknown functions. Among these isolated antigens, serum IgG antibodies for 2 isolated DNA mismatch repair enzymes, Homo sapiens mutS homolog 2 (hMSH2) and Homo sapiens postmeiotic segregation increased 1 (hPMS1), were detected in patients with pancreatic ductal adenocarcinoma and dermatomyositis (DM), and polymyositis (PM), but not in sera from healthy individuals. Immunohistochemical study demonstrated that hMSH2 and hPMS1 were over-expressed in pancreatic ductal adenocarcinoma compared to normal pancreatic ducts. These results suggested that hMSH2 and hPMS1 may be useful as CD4+ helper T cell antigens for immunotherapy of pancreatic cancer patients and that serum IgG antibodies may be useful for diagnosis of patients with pancreatic ductal adenocarcinoma and DM/PM.

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**A novel retinoid-related molecule inhibits pancreatic cancer cell proliferation by a retinoid receptor independent mechanism via suppression of cell cycle regulatory protein function and induction of caspase-associated apoptosis.**

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Retinoid-related molecules are important potential agents for the treatment of cancer. In the present study, the authors test the effect of a novel retinoid-related ligand, AGN193198 (4-[3-(1-heptyl-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-oxo-propenyl]benzoic acid), on pancreatic cancer cell proliferation and survival. AGN193198 treatment reduces BxPC-3 cell proliferation more efficiently than high-affinity retinoid acid receptor (RAR)- or retinoid X receptor (RXR)-selective retinoids. Moreover, AGN193198 does not activate transcription from RAR or RXR response elements and its effects on cell survival are not reversed by treatment with RAR- or RXR receptor-selective antagonists. These results suggest that the AGN193198-dependent inhibition of BxPC-3 cell function is not mediated via activation of the classical retinoid receptors. Cell cycle analysis of AGN193198-treated BxPC-3 cells indicates that AGN193198 causes accumulation of cells in G2/M. This change is associated with a marked reduction in regulators of S (cyclin A, cyclin-dependent kinase (cdk)2), G2/M (cyclin B1, cdk1, cdc25c) and G1 (cyclin D1, cyclin E, cdk2, cdk4) phase, and an increase in p21 and p27 level. Kinases assays reveal that cdk1, cdk2 and cdk4 activity are suppressed in AGN193198-treated cells. In addition, reduced cell proliferation is associated with enhanced procaspase (3, 8 and 9) and PARP cleavage. Z-VAD-FMK, a pancaspase inhibitor, inhibits AGN193198-dependent caspase activation and attenuates cell death.

Z-VAD-FMK inhibits PARP cleavage, but does not alter the AGN193198-dependent reduction in cell cycle regulatory protein expression and activity, suggesting that caspase activation and suppression of cell cycle regulatory protein levels are independent processes. AGN193198 produces similar responses in other pancreatic cancer cell lines including AsPC-1 and MIA PaCa-2. These studies suggest that AGN193198 may be useful for the treatment of pancreatic cancer.

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### **EUS-guided FNA of pancreatic metastases: A multicenter experience.**

Dewitt J, Jowell P, Leblanc J, McHenry L, McGreevy K, Cramer H, *et al.*

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Metastatic lesions of the pancreas are a rare but important cause of focal pancreatic lesions. The purpose of this study is to describe the EUS features, cytologic diagnoses, and clinical impact of a cohort of patients with pancreatic metastases diagnosed by EUS-guided FNA (EUS-FNA). Over a 6-year period, in a retrospective, multicenter study, patients had the diagnosis of pancreatic metastases confirmed with EUS-FNA. All examinations were performed by one of 5 experienced endosonographers. The EUS and the clinical findings of pancreatic metastases were compared with those of a cohort with primary pancreatic malignancy. Thirty-seven patients with possible metastases were identified, and 13 were excluded because of diagnostic uncertainty. The remaining 24 underwent EUS-FNA (mean passes 4.1) of a pancreatic mass without complications. Diagnoses included metastases from primary kidney (10), skin (6), lung (4), colon (2), liver (1), and stomach (1) cancer. In 4 (17%), 16 (67%), and 24 (100%) patients, EUS-FNA

provided the initial diagnosis of malignancy, tumor recurrence, and pancreatic metastases, respectively. Four (17%) metastases initially were discovered by EUS after negative (n=3) or inconclusive (n=1) CT scans. Compared with primary cancer, pancreatic metastases were more likely to have well-defined margins (46% vs. 4%) compared with irregular (94% vs. 54%;  $P<0.0001$ ) margins. No statistically significant difference between the two populations was noted for tumor size, echogenicity, consistency, location, lesion number, or number of FNA passes performed. In conclusions, pancreatic metastases are an important cause of focal pancreatic lesions and may occasionally be discovered during EUS examination after previously negative or inconclusive CT. Use of immunocytochemistry, when available, may help to confirm a suspected diagnosis. These lesions are more likely to have well-defined EUS margins compared with primary pancreatic cancer.

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### **Detection of recurrent pancreatic cancer: Comparison of FDG-PET with CT/MRI.**

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The authors determined the value of fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for the detection of recurrent pancreatic cancer in comparison to computed tomography (CT) and magnetic resonance imaging (MRI). Thirty-one patients with suspected recurrence after surgery were included. Inclusion criteria were sudden weight loss, pain or increased CA 19-9 levels. FDG-PET was performed in all patients. After visual analysis, maximal standardized uptake values (SUVmax) were determined by placing regions of interest on the pancreas bed. Additionally, all patients

underwent contrast-enhanced multidetector CT (n=14) or MR (n=17) imaging. Positive findings at FDG-PET or CT/MRI were compared to follow-up. All patients relapsed. Of 25 patients with local recurrences upon follow-up, initial imaging suggested relapse in 23 patients. Of these, FDG-PET detected 96% (22/23) and CT/MRI 39% (9/23). Local SUVmax ranged from 2.26 to 16.9 (mean, 6.06). Among 12 liver metastases, FDG-PET detected 42% (5/12). CT/MRI detected 92% (11/12) correctly. Moreover, 7/9 abdominal lesions were malignant upon follow-up of which FDG-PET detected 7/7 and CT/MR detected none. Additionally, FDG-PET detected extra-abdominal metastases in 2 patients. In patients suspected of pancreatic cancer relapse; FDG-PET reliably detected local recurrences, whereas CT/MRI was more sensitive for the detection of hepatic metastases. Furthermore, FDG-PET proved to be advantageous for the detection of nonlocoregional and extra-abdominal recurrences.

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### **The abnormalities of carbohydrate metabolism in Turner syndrome: Analysis of risk factors associated with impaired glucose tolerance.**

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An oral glucose tolerance test (OGTT) was performed in 103 patients with Turner syndrome (TS) who had normal fasting and postprandial glucose levels. The plasma glucose, insulin, C-peptide and proinsulin levels were measured every 30 min during the test. Using a homeostatic model assessment (HOMA) and a quantitative insulin sensitivity check index (QUICKI), the insulin resistance in TS patients was investigated. Diabetes mellitus and impaired glucose tolerance (IGT) were newly diagnosed in two and 18 patients

respectively. There was a significant increase in mean plasma glucose, insulin, C-peptide and proinsulin reponse during an OGTT in the IGT group in contrast to the normal glucose tolerance (NGT) group (P<0.05). There was a significant decrease in the quantitative insulin sensitivity check index (QUICKI) in the IGT group in contrast to the NGT group (P<0.05). The fasting insulin and triglyceride levels strongly predicted the 2 h glucose level during the OGTT (P<0.05). In conclusion, the oral glucose tolerance test is superior to the fasting and postprandial plasma glucose test for the early detection of abnormalities of carbohydrate metabolism in patients with Turner syndrome.

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### **Spinal cord lesions in diabetes mellitus. Somatosensory and motor evoked potentials and spinal conduction time in diabetes mellitus.**

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Diabetic neuropathy and autonomic nervous system neuropathy are recognized as the most common clinical pictures of nervous system disorders caused by diabetes mellitus (DM). Damage to the brain and the spinal cord is rare. The aim of this work is to show the importance of somatosensory and motor evoked potentials (SEP and MEP) for the early diagnosis of nervous system damage related to diabetes mellitus. The examination SEP and MEP proved and confirmed the prolongation not only of peripheral conduction time, but also of the central conduction time - especially in spinal cord structures. An assumption that spinal cord changes are connected with the decreased number of myelinated fibers able to conduct the impulses from periphery and brain cortex, respectively, has to be accepted. The results

suggest that the use of somatosensory and motor evoked potentials (SEP and MEP) examination and conduction times measurement has significance in the confirmation of unapparent lesions of the spinal cord in diabetics of both types.

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**Beta-cell function and insulin resistance evaluated by HOMA in pancreatic cancer subjects with varying degrees of glucose intolerance.**

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The authors evaluated some aspects of the pathogenesis of pancreatic cancer-associated diabetes. Using homeostasis model assessment (HOMA), the authors estimated beta-cell function (BCF) and insulin

resistance (IR) from fasting plasma glucose (FPG) and insulin in 67 normoglycemic controls and 62 age- and BMI-matched normoglycemic pancreatic cancer patients. In addition, 73 pancreatic cancer subjects with glucose intolerance were studied; 21 had impaired FPG and 51 had diabetes. BCF was similar in controls and normoglycemic pancreatic cancer subjects ( $64 \pm 5$  vs.  $78 \pm 9$ , P NS), while IR was higher in pancreatic cancer subjects with normal FPG ( $1.6 \pm 0.6$  vs.  $1.1 \pm 0.1$ ,  $P=0.002$ ). Among pancreatic cancer subjects, those with impaired FPG had markedly decreased BCF compared to those with normal FPG ( $44 \pm 5$  vs.  $78 \pm 9$ ,  $P<0.02$ ) without significant difference in IR ( $1.9 \pm 0.2$  vs.  $1.6 \pm 0.6$ , P NS). In cancer subjects, those with diabetes had markedly increased IR compared to those with impaired FPG ( $3.2 \pm 0.3$  vs.  $1.9 \pm 0.2$ ,  $P<0.0001$ ), while the BCF was similar ( $37 \pm 4$  vs.  $44 \pm 5$ ). The authors concluded that diabetes associated with pancreatic cancer is likely due to a combination of marked decline in BCF and increased insulin resistance.