Protease activation during in vivo pancreatitis is dependent upon calcineurin activation.


Department of Pediatrics, Yale University School of Medicine. New Haven, CT, USA.

The premature activation of digestive proenzymes, specifically proteases, within the pancreatic acinar cell is an early and critical event during acute pancreatitis. Previous studies demonstrate that this activation requires a distinct pathologic rise in cytosolic Ca\(^{2+}\). Further, the authors have shown that a target of aberrant Ca\(^{2+}\) in acinar cells is the Ca\(^{2+}\)/calmodulin-dependent phosphatase calcineurin (PP2B). In this study, the authors hypothesized that PP2B mediates in vivo protease activation and pancreatitis severity. To test this, pancreatitis was induced in mice over 8 hr by administrating hourly intra-peritoneal injections of the cholecystokinin analog caerulein (50 µg/kg). Treatment with the PP2B inhibitor FK506 at 1 and 8 hr post pancreatitis induction reduced trypsin activities by greater than 50% (P<0.005). Serum amylase and IL-6 was reduced by 86% and 84% relative to baseline (P<0.0005) at 8 hr, respectively. Histological severity of pancreatitis, graded based on pancreatic edema, acinar cell vacuolization, inflammation, and apoptosis was reduced early in the course of pancreatitis. Myeloperoxidase activity from both pancreas and lung was reduced by 93% and 83% relative to baseline, respectively (P<0.05). These data suggest that PP2B is an important target of the aberrant acinar cell Ca\(^{2+}\) rise associated with pathologic protease activation and pancreatitis.

Nationwide epidemiological study of severe gallstone disease in Taiwan.

Huang J, Chang CH, Wang JL, Kuo HK, Lin JW, Shau WY, Po-Huang L.

Department of Surgery, National Taiwan University Hospital. Taipei, Taiwan.

The study aimed to assess the nationwide trends in the incidence of severe gallstone disease in Taiwan among adults. A retrospective longitudinal study was conducted using Taiwan National Health Insurance Research Database collected during 1997-2005. Patients with incident severe gallstone disease (acute cholecystitis, biliary pancreatitis, acute cholangitis) and gallstone-related procedures (elective and non-elective cholecystectomy, endoscopic retrograde cholangio-pancreatography) that led to hospital admission were identified using ICD-9-CM diagnostic and procedure codes. Annual incidence rates of gallstone-related complications and procedures were calculated and their 95% confidence intervals (95% CI) were estimated assuming a Poisson distribution. The hospital admission rate for severe gallstone disease increased with advancing age and the age-standardized rate (95% CI) per 1,000 population was 0.60 (0.59-0.60) for men and 0.59 (0.59-0.60) for women. Men had a higher rate of acute cholecystitis, probably due to the substantially lower rate of elective cholecystectomy among men than women. For those aged 20-39 years, hospital admissions for all gallstone-related complications and procedures increased significantly. For those aged greater than or equal to 60 years, incidences of biliary pancreatitis, acute cholangitis, and hospital admission for gallstone receiving ERCP increased significantly without substantial change in the incidence of acute cholecystitis and despite a decreased rate of elective cholecystectomy. In conclusion, this population-based study found a substantial increase in the rate of admission for severe gallstone disease among those aged 20-39 years. Concurrently, the incidences of biliary pancreatitis and acute cholangitis have risen among those aged greater than or equal to 60 years.

Effect of diet-induced obesity on acute pancreatitis induced by administration of interleukin-12 plus interleukin-18 in mice.

Pini M, Sennello JA, Cabay RJ, Fantuzzi G.

Department of Kinesiology and Nutrition, University of Illinois at Chicago. Chicago, IL, USA.

Obesity is associated with increased severity of acute pancreatitis (AP). The authors recently developed a model of AP induced by administration of interleukin (IL) IL-12+IL-18, two cytokines that are elevated in patients with AP. In this model, severe AP develops in obese leptin-deficient ob/ob mice compared to lean littermates. In the present report, the authors evaluated the pancreatic response of diet-induced obesity (DIO) mice to IL-12+IL-18. Body weight loss and adipose tissue necrosis were more severe and prolonged in cytokine-injected DIO compared to lean mice.
Edematous AP developed in lean mice, whereas DIO mice developed necrotizing AP. Obese DIO mice developed more severe hypocalcemia, increased liver damage and a heightened acute-phase response compared to lean mice, although leukopenia and thrombocytopenia were of comparable severity in lean and DIO mice. Serum levels of IL-6, IL-10, and IL-22 were significantly higher in DIO compared to lean mice, whereas interferon-gamma and tumor necrosis factor-alpha did not differ between the two groups. In conclusion, obesity induced by high-fat diet is associated with increased disease severity and duration in the model of AP induced by administration of IL-12+IL-18.

---

(PMID: 19718789)

Inflammatory myofibroblastic tumor versus IgG4-related sclerosing disease and inflammatory pseudotumor: a comparative clinicopathologic study.

Yamamoto H, Yamaguchi H, Aishima S, Oda Y, Kohashi K, Oshiro Y, Tsuneyoshi M.

Department of Anatomic Pathology, Pathological Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Inflammatory pseudotumor (IPT) is a heterogeneous group of lesions occurring in various organs, which is histologically characterized by fibroblastic and myofibroblastic proliferation with inflammatory infiltrate. Inflammatory myofibroblastic tumor (IMT) is a neoplastic counterpart of IPT, which shows aberrant expression of ALK and its gene translocation. In contrast, the concept "IgG4-related IPT" in the lung, liver, and pancreas has recently been proposed as a member of IgG4-related sclerosing disease. In this study, the authors compared the histopathologic features with an emphasis on IgG4 expression between 22 cases of IMT and 16 cases of IgG4-related sclerosing disease, including chronic sclerosing sialadenitis (n=8), mass-forming autoimmune pancreatitis (n=3), sclerosing cholangitis (n=1), retroperitoneal fibrosis (n=2), and chronic sclerosing dacyroadenitis (n=2). Bland-looking spindle cell proliferation with fibrosis and inflammatory infiltrate of lymphocytes and plasma cells was the common morphologic feature in both lesions. Obstructive phlebitis was observed in all of the IgG4-related sclerosing lesions, but only 1/22 (4.5%) of IMT. The immunohistochemical expression of ALK was observed in 15/22 (68.2%) of IMT and 0/16 (0%) of IgG4-related sclerosing disease. The number of IgG4-positive plasma cells and the ratio of IgG4+/IgG+ plasma cells were each significantly lower in IMT than in IgG4-related sclerosing disease: mean 6.4/HPF vs. 178.3/HPF (P<0.0001), 3.0% vs. 67.5% (P<0.0001), respectively. The results suggest that IgG4 does not play an important role in the pathogenesis of IMT. In addition, the evaluation of IgG4+ plasma cells and the ratio of IgG4+/IgG+ plasma cells and the presence of obstructive phlebitis may be useful for the differential diagnosis between IMT and IgG4-related sclerosing disease.

(PMID: 19715694)

Quantitative perfusion analysis of transabdominal contrast-enhanced ultrasound of pancreatic masses and carcinomas.


Department of General, Thoracic and Vascular Surgery, School of Medicine, Dresden University of Technology, Dresden, Germany.

Preoperative differential diagnosis of pancreatic ductal adenocarcinoma (PDAC) and focal masses in patients with chronic pancreatitis (CP) can be challenging. There are fine differences in the vascularization of these lesions; ultrasound contrast agents can aid in their differentiation. The authors evaluated the value of software-aided quantitative analysis of transabdominal contrast-enhanced ultrasonography for differential diagnosis of PDAC vs. focal masses. Sixty patients for whom it was not possible to differentiate between an inflammatory focal lesion of the pancreas and a pancreatic carcinoma underwent contrast-enhanced ultrasound with a second-generation contrast agent. Time-intensity curves were obtained for all exams in two regions of interest within the lesion and within the normal pancreatic tissue. Images were processed using Axius ACQ software; the following parameters were obtained: maximum intensity, arrival time, time-to-peak, and area-under-the-curve (AUC). Absolute values and differences between the lesion and the normal tissue were evaluated. Histology analysis revealed 45 PDACs and 15 inflammatory masses in patients with CP. The time-dependent parameters (arrival time and time-to-peak) were significantly longer in PDACs compared to focal masses. Although markedly lower than in healthy pancreata, the maximum intensity and AUC parameters were not significantly different between PDACs and focal lesions in patients with CP. In cases of CP, PDAC and focal masses exhibit different perfusion patterns at a capillary level that can be visualized using the small microbubbles of ultrasound contrast agents. Contrast quantification software supplements a subjective visual assessment with objective criteria to facilitate the differential diagnosis of focal lesions in pancreatic cancer and chronic pancreatitis.
Impairment of changes in the diameter of the pancreatic portion of the superior mesenteric vein: an ultrasonographic sign of chronic pancreatitis or fibrosis.


Department of Surgery, Matsumoto Medical Center, Matsumoto Hospital. Nagano, Japan.

A new ultrasonographic technique for detecting parenchymal stiffness of the pancreas is proposed. This technique measures changes in the diameter of the origin of the superior mesenteric vein (SMV) induced by deep inspiration. The origin of the SMV has extensive attachments to the pancreatic parenchyma; therefore, both physiologic enlargement and shrinkage of the venous lumen cannot occur without changes in the shape of the surrounding parenchyma. Therefore, increased parenchymal stiffness due to chronic pancreatitis (CP) may result in impaired changes in the venous diameter. To confirm this hypothesis, patients with CP and those with a normal pancreas were examined in this study. Twelve patients in each group were examined. Images of the origin of the SMV were obtained with a commercial ultrasound system. The smallest diameter of the SMV was measured during normal breathing. The patients were then asked to take a deep breath to increase the portal blood pressure followed immediately by the same measurements as performed during normal breathing, and the ratio of the change was calculated. In the normal group, the diameter of the SMV changed by 79.5±43.8% (mean±SD), whereas a change of 1.4±7.3% was observed in the CP group. The difference between the two groups was statistically significant (P<0.0001). In conclusion, the physiologic change in the diameter of the origin of the SMV enhanced by deep inspiration may reflect the stiffness of the pancreatic parenchyma. Therefore, detection of an impaired diameter change may be useful for screening of CP.

(PMID: 19707261)

Delayed release pancrelipase for treatment of pancreatic exocrine insufficiency associated with chronic pancreatitis.

Krishnamurty DM, Rabiee A, Jagannath SB, Andersen DK.

Department of Medicine, Johns Hopkins University School of Medicine. Baltimore, MD, USA.

Pancreatic enzyme supplements (PES) are used in chronic pancreatitis (CP) for correction of pancreatic exocrine insufficiency (PEI) as well as pain and malnutrition. The use of porcine pancreatic enzymes for the correction of exocrine insufficiency is governed by the pathophysiology of the disease as well as pharmacologic properties of PES. Variability in bioequivalence of PES has been noted on in vitro and in vivo testing and has been attributed to the differences in enteric coating and the degree of micro-encapsulation. As a step towards standardizing pancreatic enzyme preparations, the Food and Drug Administration now requires the manufacturers of PES to obtain approval of marketed formulations by April 2010. In patients with treatment failure, apart from evaluating drug and dietary interactions and compliance, physicians should keep in mind that patients may benefit from switching to a different formulation. The choice of PES (enteric coated versus non-enteric coated) and the need for acid suppression should be individualized. There is no current standard test for evaluating adequacy of therapy in CP patients and studies have shown that optimization of therapy based on symptoms may be inadequate. Goals of therapy based on overall patient presentation and specific laboratory tests rather than mere correction of steatorrhea are needed.

(PMID: 19722229)

Survival analysis after pancreatic resection for ampullary and pancreatic head carcinoma: An analysis of clinicopathological factors.


Division of Surgery and Cancer, HPB Unit, Hammersmith Hospital, Imperial College. London, England, United Kingdom.

Surgery remains the only curative option for the treatment of pancreatic and ampullary carcinomas. The authors examined the survival differences between ampullary and pancreatic head carcinomas after pancreaticoduodenectomy. They retrospectively reviewed the data of patients with ampullary or pancreatic head adenocarcinoma undergoing curative resection during a 6-year period prior to 2000. A total of 104 patients underwent pancreaticoduodenectomy for pancreatic head and ampullary carcinomas (n=65 and n=39, respectively). Histologically, pancreatic cancer was worse, with more lymph node involvement and more positive resection margins and vascular and perineural invasions than found in ampullary carcinoma. The median disease-free and overall survival rates were significantly better for ampullary cancer when compared with pancreatic cancer: 17 vs. 9 months (P=0.001) and 35 vs. 24 months (P=0.006), respectively. The actuarial 5-year disease-free and overall survival rates were 4.4% and 10.5%,
respectively, for pancreatic carcinoma and 27.9% and 31.8%, respectively, for ampullary carcinoma. Multivariate analysis showed that microscopic resection margin involvement (P = 0.02) and involvement of over three nodes (P < 0.001) were significant factors affecting the overall survival for pancreatic and ampullary carcinomas, respectively. In this study, patients with ampullary carcinoma have a better prognosis and survival than those with pancreatic carcinoma.

J Clin Oncol 2009 Aug 31. (PMID: 19720928)

Centralization of Cancer Surgery: Implications for Patient Access to Optimal Care.

Stitzenberg KB, Sigurdson ER, Egleston BL, Starkey RB, Meropol NJ et al.

Department of Surgical Oncology, Biostatistics, and Medical Oncology, University of Pennsylvania, Philadelphia, PA, USA

The volume-outcomes relationship has led many to advocate centralization of cancer procedures at high volume hospitals (HVH). The authors hypothesized that in response cancer surgery has become increasingly centralized and that this centralization has resulted in increased travel burden for patients. Using 1996 to 2006 discharge data from NY, NJ, PA, all patients 18, or more, years old treated with extirpative surgery for colorectal, esophageal, or pancreatic cancer were examined. Patients and hospitals were geocoded. Annual hospital procedure volume for each tumor site was examined, and multiple quantile and logistic regressions were used to compare changes in centralization and distance traveled. Five-thousand two-hundred seventy-three esophageal, 13,472 pancreatic, 202,879 colon, and 51,262 rectal procedures were included. A shift to HVH occurred to varying degrees for all tumor types. The odds of surgery at a low volume hospital decreased for esophagus, pancreas and colon: per year odds ratios were 0.87 (95% CI, 0.85 to 0.90), 0.85 (95% CI, 0.84 to 0.87), and 0.97 (95% CI, 0.97 to 0.98). Median travel distance increased for all sites: esophagus 72%, pancreas 40%, colon 17%, and rectum 28% (P < 0.0001). Travel distance was proportional to procedure volume (P < 0.0001). The majority of the increase in distance was attributable to centralization. In conclusion, there has been extensive centralization of complex cancer surgery over the past decade. While this process should result in population-level improvements in cancer outcomes, centralization is increasing patient travel. For some subsets of the population, increasing travel requirements may pose a significant barrier to access to quality cancer care.

Document URL: http://www.joplink.net prev/200909/alerts.html