PANCREAS ALERTS

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The role of Doppler sonography in predicting severity of acute pancreatitis.

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The authors aimed to investigate the role of Doppler sonography (DUS) examination of major abdominal arteries in predicting severity of acute pancreatitis (AP). Twenty-nine patients diagnosed with AP and 14 controls were blindly and prospectively evaluated with Doppler sonography. Disease severity was defined clinically according to acute physiology and chronic health evaluation (APACHE II) score and was classified as severe for APACHE II score equal to, or greater than, 8. DUS examination included the measurement of peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility index (PI), and resistance index (RI) of the celiac artery (CA) and superior mesenteric artery (SMA). Statistical analysis included Mann-Whitney U test, Student t test, and receiver operating characteristic curve analysis. Twelve patients had severe AP and 17 had mild AP. PSV, EDV, and PI of the CA and RI of the SMA were higher in the severe AP group than in the mild AP and control groups ($P<0.001$ and $P<0.0001$, respectively). The sensitivity and specificity were 100% and 94%, respectively, for a 87 cm/second CA PSV cutoff value, 75% and 100%, respectively, for a 22 cm/second CA EDV cutoff value, 92% and 82%, respectively, for a 1.29 CA PI cutoff value, and 100% and 100%, respectively, for a 0.86 SMA RI cutoff value. DUS can be useful in predicting the severity of AP in the early period of admission phase of the disease.

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A survey of current surgical treatment of acute gallstone disease in the west of Scotland.

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National guidelines exist for the treatment of acute gallstone pancreatitis, but not for the management of acute cholecystitis (AC). The authors aimed to establish the preferred management of uncomplicated AC and adherence to guidelines for the management of mild gallstone pancreatitis in the west of Scotland. A postal survey of all 100 consultant general surgeons in the west of Scotland. Sixty-seven of 71 responses received were suitable for analysis. For uncomplicated AC, 24 (36%) perform urgent laparoscopic cholecystectomy (LC), 16 (24%) perform same admission LC after clinical improvement. Twenty-three (34%) perform interval LC after discharge. Within this group, 9 surgeons (13%) manage AC conservatively due to insufficient operating time or equipment when on call. In mild gallstone pancreatitis, 33 (49%) perform same admission LC, 13 (19%) perform sphincterotomy, 3 (4.5%) perform one of these depending on the patient and 6 (9.5%) refer to a colleague with an interest in upper gastrointestinal surgery. The majority of surgeons (over 60%) manage AC with same admission LC. Of those who do not, more than a third report lack of resources as being the reason. The majority of surgeons in the West of Scotland manage mild gallstone pancreatitis in accordance with current guidelines.

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Immunohistochemical localization of interleukin-6 in human pancreatitis.

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The aim of the study was to identify immunohistochemically the localization of interleukin (IL)-6 in normal pancreas and in chronic pancreatitis (CP). Samples of tissues of normal pancreas (n=5) and CP (n=16), were verified histopathologically and then IL-6 was localized by immunohistochemical staining using the monoclonal antihuman IL-6 antibody and test LSAB2-HRP to visualize IL-6/Ab complexes. In slices of the pancreas, derived from patients with CP, a much stronger immunohistochemical reaction was noticed as compared with controls specimens. IL-6 was localized in exocrine, islet cells and ducts cells of the pancreas. Interestingly, this cytokine was detected in cytoplasm and very close to nucleus. Moreover, in cases of CP with inflammatory infiltration, there were a markedly stronger IL-6 expression, than that observed in specimens without infiltrate. In conclusion, the results presented herein clearly demonstrated a moderate and strong expression of IL-6 in exocrine and endocrine cells of patients with CP. These observations provide further support for the existence of local immune-pancreatic interactions.

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Efficacy of endoscopic ultrasound in characterizing mass lesions in chronic pancreatitis.

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The aim of this study was to determine the influence of endoscopic ultrasound (EUS) in the detection of chronic pancreatitis and identification of pancreatic masses suspected by other radiographic imaging modalities in such a clinical background. Retrospective analysis was performed on 105 consecutive pancreatic EUS examinations in an 18-month period at a single tertiary care referral center. Analysis included 75 patients with a suspected pancreatic mass by computerized axial tomography, magnetic resonance imaging, ultrasound, or endoscopic retrograde cholangiopancreotography. All patients underwent EUS examination and if a mass was visualized, fine-needle aspiration biopsy was performed. Patients underwent either surgical exploration or clinical and radiographic follow-up for 6 months to confirm EUS findings. Chronic pancreatitis was suspected in 53 individuals by clinical or radiographic methods. Using standard EUS parenchymal and ductal criteria, chronic pancreatitis was confirmed in 41 (77%) of patients. In 33 patients with chronic pancreatitis detected by EUS, initial referral was for pancreatic mass. Twenty-eight (85%) patients had an actual mass and the remainder were false-positive clinical findings. Thirty-two percent of pancreatic masses in chronic pancreatitis were found to be malignant adenocarcinoma and the rest were inflammatory in nature. Subset analysis showed EUS-fine-needle aspiration of solid lesions to have a sensitivity and specificity of 87.9% and 100%, respectively. Detection of cystic lesions had a sensitivity and specificity of 88.5% and 100%, respectively. EUS is superior to other radiographic modalities in the determination of chronic pancreatitis and detection of mass lesions.

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Alcohol dehydrogenase (ADH) isoenzymes and aldehyde dehydrogenase (ALDH) activity in the sera of patients with pancreatic cancer.

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Numerous experiments have shown that alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are present in cells of various cancer and can play role in carcinogenesis. In previous investigations the authors have found elevated levels of alcohol dehydrogenase class III activity in pancreatic cancer cells. It can suggest that these changes may be reflected by enzyme activity in the serum. The authors have measured the activity of alcohol dehydrogenase iso-enzymes, and aldehyde dehydrogenase in the sera of patients with pancreatic cancer. Serum samples were taken for routine biochemical investigation from 56 patients with pancreatic cancer before treatment. Total ADH activity was measured by photometric method with p-nitrosodimethylaniline (NDMA) as a substrate, and ALDH activity by the fluorometric method with 6-methoxy-2-naphtaldehyde as a substrate. For the measurement of the activity of class I isoenzymes, the authors employed the fluorometric methods, with class-specific fluorogenic substrates. The activity of class III alcohol dehydrogenase was measured by the photometric method with n-octanol and class IV with m-nitrobenzaldehyde as a substrate. A statistically significant increase of class III alcohol dehydrogenase iso-enzymes was found in the sera of cancer patients. The median activity of this class isoenzyme in the total cancer group increased about 22% (13.52 mU/L) in the comparison with the control level (11.08 mU/L). The total alcohol dehydrogenase activity was significantly higher (19.7%) among patients with cancer than healthy ones. The activities of other tested ADH isoenzymes and total ALDH were unchanged. The activity of the class I ADH isoenzyme was significantly higher in the sera of drinkers with pancreatic cancer than non-drinkers. The increased total activity of alcohol dehydrogenase and class III isoenzyme in the sera of patients with pancreatic cancer can be caused by release of this isoenzyme from cancer cells.

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Loss of ONECUT1 expression in human pancreatic cancer cells.

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ONECUT1 (HNF-6) is the prototype of a new class of homeodomain transcription factors, that controls the development of pancreatic ducts during mouse development. In the present study, the role of ONECUT1 and its targeted genes TCF2, PKHD1 and CYS1 was analyzed in human pancreatic ductal adenocarcinoma (PDAC). mRNA levels of ONECUT1, TCF2, PKHD1 and CYS1 were measured in pancreatic tissues and pancreatic cancer cell lines by quantitative reverse-transcriptase polymerase chain reaction (QRT-PCR). Protein expression of ONECUT1 and TCF2 was assessed in pancreatic tissues by immunohistochemistry. ONECUT1 was transfected into Panc-1 and T3M4 pancreatic cancer cells and its effects on anchorage-dependent and -independent growth as well as invasion and adhesion were analyzed. Median mRNA levels of ONECUT1, TCF2, PKHD1 and CYS1 were 7.7-, 2.0-, 5.7- and 3.8-fold higher in normal tissues than in PDAC tissues. ONECUT1 protein was expressed in normal acinar and ductal cells, but neither in the cancer cells of PDAC tissues nor in 7 of 8 cultured pancreatic cancer cell lines. There was a significant positive correlation between ONECUT1 and TCF2, CYS1, and PKHD1 mRNA levels in PDAC tissues. Transfection of ONECUT1 into pancreatic cancer cells

resulted in up-regulation of the target gene TCF2, a reduction in invasiveness, but no change in adhesion or growth. In conclusion, ONECUT1 expression is lost in pancreatic cancer cells, suggesting a tumor suppressor function in this malignancy.

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GABA(B) receptor is a novel drug target for pancreatic cancer.

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Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer death. Smoking, diabetes, and pancreatitis are risk factors. It has been shown that the growth of PDAC and pancreatic duct epithelial cells is regulated by beta-adrenoreceptors (beta-ARs). The activity of beta-ARs in the central nervous system is counteracted by gamma-aminobutyric acid (GABA) via GABA(B) receptor-mediated inhibition of adenylyl cyclase. The aim of the study was to investigate if GABA(B)R inhibits beta-AR signaling in PDAC and pancreatic duct epithelial cells, thus blocking driving forces of cancer progression, such as cell proliferation and cell migration. Intracellular cAMP was measured by immunoassays, DNA synthesis by BrdU incorporation assays, activation of ERK1/2 by ERK activation assays, and Western blots and metastatic potential by cell migration assays in the human PDAC cell lines PANC-1 and BXPC-3 and immortalized human pancreatic duct epithelial cells HPDE6-C7. The expression of norepinephrine, PKAR(IIalpha), and GABA in PDAC microarrays was assessed by immunohistochemistry. Stimulation of the GABA(B)R by GABA or baclofen inhibited isoproterenol-induced cAMP signaling below base levels. ERK1/2 activity in response to isoproterenol was blocked by GABA, an effect enhanced by transient overexpression of the GABA(B)R and abolished by GABA(B)R knockdown. DNA synthesis and cell migration were stimulated by isoproterenol, responses blocked by GABA and baclofen. Norepinephrine and PKAR(IIalpha) were overexpressed while GABA was underexpressed in human PDAC tissue arrays. The data suggest the stimulation of GABA(B)R signaling as a novel target for the treatment and prevention of pancreatic cancer.

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Tissue angiotensin-converting enzyme inhibitors for the prevention of cardiovascular disease in patients with diabetes mellitus without left ventricular systolic dysfunction or clinical evidence of heart failure: a pooled meta-analysis of randomized placebo-controlled clinical trials.

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The aim of this study was to determine the role of tissue angiotensin-converting enzyme (ACE) inhibitors in the prevention of cardiovascular disease in patients with diabetes mellitus without left ventricular systolic dysfunction or clinical evidence of heart failure in randomized placebo-controlled clinical trials using pooled meta-analysis techniques. Randomized placebo-controlled clinical trials of at least 12 months duration in patients with diabetes mellitus without left ventricular systolic dysfunction or heart failure who had experienced a prior cardiovascular event or were at high cardiovascular risk were selected. A total of 10,328 patients (43,517 patient-years) from four selected trials were used for meta-analysis. Relative risk estimations were made using data pooled from the selected trials and statistical significance was determined using the Chi-squared test (two-sided alpha error

less than 0.05). The number of patients needed to treat was also calculated. Results: Tissue ACE inhibitors significantly reduced the risk of cardiovascular mortality by 14.9% (P=0.022), myocardial infarction by 20.8% (P=0.002) and the need for invasive coronary revascularization by 14% (P=0.015) when compared to placebo. The risk of all-cause mortality also tended to be lower among patients randomized to tissue ACE inhibitors, whereas the risks of stroke and hospitalization for heart failure were not significantly affected. Treating about 65 patients with tissue ACE inhibitors for about 4.2 years would prevent one myocardial infarction, whereas treating about 85 patients would prevent one cardiovascular death. Conclusion: Pooled meta-analysis of randomized placebo-controlled trials suggests that tissue ACE inhibitors modestly reduce the risk of myocardial infarction and cardiovascular death and tend to reduce overall mortality in diabetic patients without left ventricular systolic dysfunction or heart failure.

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Association of TCF7L2 polymorphisms with susceptibility to type 2 diabetes in 4,087 Japanese subjects.

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Transcription factor 7-like 2 (TCF7L2) has been shown to be associated with type 2 diabetes mellitus in multiple ethnic groups. Regarding the Asian population, Horikoshi *et al*. (Diabetologia 2007; 50:747-51) and Hayashi *et al*. (Diabetologia 2007; 50:980-4) reported that single nucleotide polymorphisms (SNPs) in TCF7L2 were associated with type 2 diabetes in the Japanese population, while contradictory results were reported for Han Chinese populations. The aim of this study was to investigate the associations of the TCF7L2 gene with type 2 diabetes using a relatively large sample size: 2,214 Japanese individuals with type 2 diabetes and 1,873 normal controls. The minor alleles of rs7903146, rs11196205, and rs12255372 showed significant associations with type 2 diabetes (OR=1.48, $P=2.7\times10^{-4}$; OR=1.39, $P=4.6\times10^{-4}$; OR=1.70, $P=9.8\times10^{-5}$, respectively) in the combined sample sets. However, neither rs11196218 nor rs290487 showed a significant association. These results indicate that TCF7L2 is an important susceptibility gene for type 2 diabetes in the Japanese population.

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