PANCREAS ALERTS

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Chronic alcohol intake increases the severity of pancreatitis induced by acute alcohol administration, hyperlipidemia and pancreatic duct obstruction in rats.

Grauvogel J, Daemmrich TD, Ryschich E, Gebhard MM, Werner J.

Department of Surgery, University of Heidelberg. Heidelberg, Germany.

The mechanism of alcoholic pancreatitis is still unknown. It is of special interest why only about 5% of all alcoholics develop an episode of pancreatitis. The authors evaluated the role of long-term alcohol intake in the pathogenesis of alcoholic pancreatitis in rats. To evaluate the effect of long-term alcohol intake, rats were fed either a Lieber-DeCarli control diet (CD) or a Lieber-DeCarli alcohol diet (AD) for 6 weeks. Then, rats were infused over 2 h with either Ringer's solution (CO) or ethanol (E). In additional animals, alcoholic pancreatitis was induced by ethanol combined with hyperlipidemia and temporary pancreatic duct obstruction (EFO). Controls received Ringer's solution combined with hyperlipidemia and temporary pancreatic duct obstruction (RFO). Intravital microscopy (pancreatic perfusion and leukocyte adhesion), alcohol concentrations, amylase, lipase, cholesterine and triglyceride levels in plasma, myeloperoxidase activity and histology were evaluated at different time intervals. In those animals which received the Lieber-DeCarli control diet, capillary perfusion was reduced in the E group and further reduced in the EFO group as compared to the controls (CO, RFO; $P<0.01$). Leukocyte adhesion was significantly increased in rats receiving E ($P<0.01$), and was further increased in the combination group EFO ($P<0.01$). EFO induced histologically evident acute pancreatitis. The additional administration of a long-term alcohol diet further increased microcirculatory disturbances and pancreatic injury significantly (EFO-AD > EFO-CD). In conclusion, this study shows that alcoholic pancreatitis is induced by the combination of ethanol and individual cofactors. Chronic alcohol abuse intensifies these changes. Therefore, long-term alcohol intake seems to be a major factor in the pathogenesis of alcoholic pancreatitis.

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Fatty acid composition of plasma lipid classes in chronic alcoholic pancreatitis.

Marosvolgyi T, Horvath G, Dittrich A, Cseh J, Lelovics Z, Szabo E, *et al.*

Department of Paediatrics, University of Pecs. Pecs, Hungary.

Supplementation of n-3 long-chain polyunsaturated fatty acids (LCPUFA) is considered as adjuvant therapy in acute pancreatitis. The authors investigated plasma fatty acid status in chronic pancreatitis (CP). Patients with alcoholic CP (n=56, gender: 33/23 male/female, age: 60.0 [14.0] years (median [IQR]), who reported giving up alcohol consumption several years ago and 51 control subjects were included into the study. The fatty acid composition of plasma phospholipids (PL), triacylglycerols (TG) and sterol esters (STE) was analyzed. The sum of mono-unsaturated fatty acids was significantly higher in patients with CP than in controls (PL: 12.83 [3.35] *vs.* 12.20 [1.95], TG: 40.51 [6.02] *vs.* 37.52 [5.80], STE: 20.58 [7.22] *vs.* 17.54 [3.48], CP *vs.* control, % weight/weight, median [IQR], $P<0.05$). Values of arachidonic acid were significantly lower in patients with CP than in controls (PL: 10.57 [3.56] *vs.* 11.66 [3.25], STE: 8.14 [2.63] *vs.* 9.24 [2.86], $P<0.05$). Values of eicosapentaenoic acid and docosahexaenoic acid did not differ and there was no difference in the ratio of n-3 to n-6 LCPUFA. In conclusion, these data do not furnish evidence for the supplementation of n-3 LCPUFA to the diet of CP patients in relatively good clinical condition.

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Acute pancreatitis: imaging utilization practices in an urban teaching hospital. Analysis of trends with assessment of independent predictors in correlation with patient outcomes.

Mortele KJ, Ip IK, Wu BU, Conwell DL, Banks PA, Khorasani R.

Center for Evidence Based Imaging, Division of Abdominal Imaging and Intervention, Brigham and Women's Hospital, Harvard Medical School. Boston, MA. USA.

The authors aimed to evaluate imaging utilization trends in patients with acute pancreatitis (AP) and to assess independent predictors of radiology usage in relation to patient outcomes. Institutional review board approval was obtained for this HIPAA-compliant study; written informed consent was waived. AP-related radiologic studies in 252 patients admitted for AP between June 2005 and December 2007 were collected during and for a 1-year period after

hospitalization. Clinical data were collected from patients' medical records, while imaging data were obtained from the radiology information system. Linear regression models were used to investigate predictors and time trends of imaging utilization, after adjustment for confounders. Patient outcomes, measured by using mortality, intensive care unit admission, need for surgical intervention, organ failure, and persistent systemic inflammatory response syndrome, were evaluated by using logistic regression. Results: Mean utilization was 9.9 radiologic studies per patient (95% confidence interval: 7.5, 12.3), with relative value unit (RVU) of 7.8 (95% confidence interval: 6.3, 9.4). Utilization was highest on day 0, declining rapidly by day 4; 53% of imaging occurred during initial hospitalization. Chest radiography (38%) and abdominal computed tomography (CT) (17%) were the most commonly performed studies. Patients with longer hospital stay (P=0.001), higher Acute Physiology and Chronic Health Evaluation II score (P=0.0012), higher pain levels (P=0.003), drug-induced AP (P=0.002), and prior episodes of AP (P<0.001) underwent significantly more radiologic studies. After adjustment for confounders, a 2.5-fold increase in the use of high-cost (CT and magnetic resonance imaging) examinations and a 1.4-fold increase in RVUs per case-mix-adjusted admissions (P<0.05) were observed during the 2.5-year study period. This increased use was not associated with improvement in patient outcomes. In conclusion, AP severity explained substantial variation in imaging utilization. After case-mix adjustment for severity and other patient level factors, there was still increasing use over the course of time without notable improvement in patient outcomes.

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Practical guidelines for aute pancreatitis.

Pezzilli R, Zerbi A, Di Carlo V, Bassi C, Delle Fave GF.

Italian Association for the Study of the Pancreas.

The following is a summary of the official guidelines of the Italian Association for the Study of the Pancreas regarding the medical, endoscopic and surgical management of acute pancreatitis. Statements: Clinical features together with elevation of the plasma concentrations of pancreatic enzymes are the corner-stones of diagnosis (recommendation A). Contrast-enhanced computed tomography (CT) provides good evidence for the presence of pancreatitis (recommendation C) and it should be carried out 48-72 h after the onset of symptoms in patients with predicted severe pancreatitis. Severity assessment is essential for the selection of the proper initial treatment in the management of acute pancreatitis (recommendation A) and should be done using the APACHE II score, serum C-reactive protein and CT assessment (recommendation C). The etiology of acute pancreatitis should be able to be determined in at least 80% of cases (recommendation B). An adequate volume of intravenous fluid should be administered promptly to correct the volume deficit and maintain basal fluid requirements (recommendation A); analgesia is crucial for the correct treatment of the disease (recommendation A). Enteral feeding is indicated in severe necrotizing pancreatitis and it is better than total parenteral nutrition (recommendation A). The use of prophylactic broad-spectrum antibiotics reduces infection rates in CT-proven necrotizing pancreatitis (recommendation A). Infected pancreatic necrosis in patients with clinical signs and symptoms of sepsis is an indication for intervention, including surgery and radiological drainage (recommendation B). The participants agreed to revise the guidelines every 3 years in order to re-evaluate each question on the management of acute pancreatitis patients according to the most recent literature.

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Role of protein kinase C in caerulein induced expression of substance P and neurokinin-1-receptors in murine pancreatic acinar cells.

Koh YH, Tamizhselvi R, Moochhala S, Bian J, Bhatia M.

Department of Pharmacology, National University of Singapore. Singapore, Singapore.

Substance P (SP) is involved in the pathophysiology of acute pancreatitis (AP) via binding to its high affinity receptor, neurokinin-1-receptor (NK1R). An up-regulation of SP and NK1R expression was observed in experimental AP and in caerulein-stimulated pancreatic acinar cells. However, the mechanisms that lead to this up-regulation are not fully understood. In this study, the authors showed the role of protein kinase C (PKC) in caerulein-induced SP and NK1R production in isolated mouse pancreatic acinar cells. Caerulein (10^{-7} M) stimulation rapidly activated the conventional PKC-alpha and novel PKC-delta as observed by the phosphorylation of these molecules. Pre-treatment of pancreatic acinar cells with Gö6976 (1-10 nM) and rottlerin (1-10 μM) inhibited PKC-alpha and PKC-delta phosphorylation respectively, but not the other way round. At these concentrations used, PKC-alpha and PKC-delta inhibition reversed the caerulein-induced up-regulation of SP and NK1R, indicating an important role of PKCs in the modulation of SP and NK1R expression. Further experiments looking into signaling mechanisms showed that treatment of pancreatic acinar cells with both Gö6976 and rottlerin inhibited the activation of ERK1/2 and JNK. Inhibition of PKC-alpha or PKC-delta also affected caerulein-induced transcription factor activation, as represented by NF-kappa B and AP-1 DNA binding activity. The

findings in this study suggested that PKC is upstream of the MAPKs and transcription factors, which then lead to the up-regulation of SP/NK1R expression in caerulein treated mouse pancreatic acinar cells.

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Combined bicarbonate conductance-impairing variants in CFTR and SPINK1 are associated with chronic pancreatitis in patients without cystic fibrosis.

Schneider A, Larusch J, Sun X, Aloe A, Lamb J, Hawes R, *et al.*

Department of Medicine, University of Pittsburgh. Pittsburgh, PA, USA.

Idiopathic chronic pancreatitis (ICP) is a complex inflammatory disorder associated with multiple genetic and environmental factors. In individuals without cystic fibrosis (CF), variants of CFTR that inhibit bicarbonate conductance but maintain chloride conductance might selectively impair secretion of pancreatic juice, leading to trypsin activation and pancreatitis. The authors investigated whether sequence variants in the gene encoding the pancreatic secretory trypsin inhibitor, SPINK1, further increase the risk of pancreatitis in these patients. The authors screened patients with ICP (sporadic or familial) and controls for variants in SPINK1 associated with chronic pancreatitis (CP) risk (in exon 3) and in all 27 exons of CFTR. The final study group included 53 patients with sporadic ICP, 27 probands with familial ICP, and 150 unrelated controls, plus 503 controls for limited genotyping. CFTR wild-type (wt) and p.R75Q were cloned and expressed in HEK293 cells and relative conductances of HCO_3^- and Cl^- were measured. SPINK1 variants were identified in 36% of subjects and 3% controls (odds ratio [OR]=16.5). One variant of CFTR that has not been associated with CF, p.R75Q, was found in 16% of subjects and 5.4% controls (OR=3.4). Co-inheritance of CFTR p.R75Q and SPINK1 variants occurred in 8.75% of patients and 0.15% controls (OR=62.5). Patch-clamp recordings of cells that expressed CFTR p.R75Q demonstrated normal chloride currents but significantly reduced bicarbonate currents (P=0.0001). The CFTR variant p.R75Q causes a selective defect in bicarbonate conductance and increases risk for pancreatitis. Co-inheritance of CF-associated, and some not associated, CFTR variants with SPINK1 variants significantly increase risk of ICP.

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Soft drinks, sweetened beverages and risk of pancreatic cancer.

Gallus S, Turati F, Tavani A, Polesel J, Talamini R, Franceschi S, La Vecchia C.

Department of Epidemiology, Institute of Pharmacological Researches "Mario Negri". Milan, Italy.

Soft drinks usually contain sugar and caffeine that might influence pancreatic carcinogenesis. The authors considered the association between carbonated drink consumption and pancreatic cancer risk in an Italian case-control study conducted in 1991-2008 on 326 pancreatic cancer cases and 652 matched controls. The authors also combined the results from all the studies on soft drinks or sweetened beverages and pancreatic cancer published before June 2010, using a meta-analytic approach. In the case-control study, compared with non-drinkers, the multivariate odds ratio was 1.02 (95% confidence interval, CI, 0.72-1.44) for carbonated drink consumers and 0.89 (95% CI 0.53-1.50) for regular consumers (at least one drink/day). Besides their study, from the literature search, the authors identified 4 other case-control (1,919 cases) and 6 cohort studies (2,367 cases). The pooled relative risks (RR) for soft drink consumers *vs.* non-consumers were 0.97 (95% CI 0.81-1.16) for case-control, 1.05 (95% CI 0.94-1.17) for cohort, and 1.02 (95% CI 0.93-1.12) for all studies. The pooled RRs for heavy drinkers were 1.08 (95% CI 0.73-1.60) for case-control, 1.21 (95% CI 0.90-1.63) for cohort, and 1.16 (95% CI 0.93-1.45) for all studies. In conclusion, soft drink consumption is not materially related to pancreatic cancer risk.

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Chromosome 3p alterations in pancreatic endocrine neoplasia.

Amato E, Barbi S, Malpeli G, Bersani S, Pelosi G, Capelli P, Scarpa A.

ARC-NET Center for Applied Research on Cancer, Hospital Concern and University School of Medicine. Verona, Italy.

Pancreatic endocrine tumors (PET) are rare neoplasms classified as functioning (F-PET) or non-functioning (NF-PET) according to the presence of a clinical syndrome due to hormonal hypersecretion. PETs show variable degrees of clinical aggressiveness and loss of chromosome 3p has been suggested to be associated with an advanced stage of disease. The authors assessed chromosome 3p copy number in 113 primary PETs and 32 metastases by fluorescence in situ hybridization (FISH) using tissue microarrays. The series included 56 well-differentiated endocrine tumors (WDET), 62 well-differentiated endocrine carcinomas (WDEC), and 6 poorly differentiated endocrine carcinomas (PDEC). Chromosome 3p alterations were found in 23/113 (20%) primary tumors, with losses being predominant over gains (14% *vs.* 6%). Loss of 3p

was found in 5/55 (9%) WDET, 11/52 (21%) WDEC, and never in PDEC. Gains of 3p were detected in 4/55 (7%) WDET, no WDEC, but notably in 3/6 (50%) PDEC (OR 23.6; P=0.003). Metastases were more frequently monosomic for 3p compared to primary tumors (OR 3.6; P=0.005). Monosomy was significantly associated with larger tumor size, more advanced tumor stage, and metastasis. No association was found with survival. Chromosome 3p copy number alterations are frequent events in advanced stage PET, with gains prevailing in PDEC while losses are more frequent in WDEC, supporting the view that a specific pattern of alterations are involved in these diverse disease subtypes.

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Diabetes mellitus abrogates erythropoietin-induced cardioprotection against ischemic-reperfusion injury by alteration of the RISK/GSK-3beta signaling.

Ghaboura N, Tamareille S, Ducluzeau PH, Grimaud L, Loufrani L, Croué A, *et al.*

Protection and myocardial remodeling (UPRES EA 3860), Faculy of Medicine, University of Angers. Angers, France.

Recent studies reported cardioprotective effects of erythropoietin (EPO) against ischemia-reperfusion (I/R) injury through activation of the reperfusion injury salvage kinase (RISK) pathway. As RISK has been reported to be impaired in diabetes and insulin resistance syndrome, the authors examined whether EPO-induced cardioprotection was maintained in rat models of type 1 diabetes and insulin resistance syndrome. Isolated hearts were obtained from three rat cohorts: healthy controls, streptozotocin (STZ)-induced diabetes, and high-fat diet (HFD)-induced insulin resistance syndrome. All hearts underwent 25 min ischemia and 30 min or 120 min reperfusion. They were assigned to receive either no intervention or a single dose of EPO at the onset of reperfusion. In hearts from healthy controls, EPO decreased infarct size (14.36±0.60 and 36.22±4.20% of left ventricle in EPO-treated and untreated hearts, respectively, P<0.05) and increased phosphorylated forms of Akt, ERK1/2, and their downstream target GSK-3beta. In hearts from STZ-induced diabetic rats, EPO did not decrease infarct size (32.05±2.38 and 31.88±1.87% in EPO-treated and untreated diabetic rat hearts, respectively, NS) nor did it increase phosphorylation of Akt, ERK1/2, and GSK-3beta. In contrast, in hearts from HFD-induced insulin resistance rats, EPO decreased infarct size (18.66±1.99 and 34.62±3.41% in EPO-treated and untreated HFD rat hearts, respectively, P<0.05) and increased phosphorylation of Akt, ERK1/2, and GSK-3beta. Administration of GSK-3beta inhibitor SB216763 was cardioprotective in healthy and diabetic hearts. STZ-induced diabetes abolished EPO-induced cardioprotection against I/R injury through a disruption of upstream signaling of GSK-3beta. In conclusion, direct inhibition of GSK-3beta may provide an alternative strategy to protect diabetic hearts against I/R injury.

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Roles of beta2- and beta3-adrenoceptor polymorphisms in hypertension and metabolic syndrome.

Masuo K.

Nucleus Network Ltd.. Melbourne, VIC, Australia.

Hypertension, diabetes mellitus (especially type 2 diabetes mellitus), metabolic syndrome and obesity are rapidly growing public health problems. Sympathetic nerve activation is observed in obesity, hypertension and diabetes mellitus, which have strong genetic as well as environmental determinants. Reduced energy expenditure and resting metabolic rate are predictive of weight gain, and the sympathetic nervous system participates in regulating energy balance through thermogenesis. The thermogenic effects of catecholamines in obesity have been mainly mediated via the beta2- and beta3-adrenergic receptors in humans. Further, beta2-adrenoceptors importantly influence vascular reactivity and may regulate blood pressure. Genetic polymorphistns of the beta-adrenoceptor gene have been shown to alter the function of several adrenoceptor subtypes and thus to modify the response to catecholamine. Beta2-adrenoceptor polymorphisms (Arg16Gly, Gln27Glu, and Thr164Ile) have been studied in relation to hypertension. Genetic variations in the beta3-adrenoceptor (i.e. Try64Arg variant) are also associated with both obesity and hypertension. However, the precise relationships of the polymorphisms of beta2- and beta3-adrenoceptor genes with sympathetic nervous system activity, hypertension, and metabolic syndrome have not been fully clarified. This paper will discuss the current topics involving the influence of the sympathetic nervous system and beta2- and beta3- adrenoceptor polymorphisms in hypertension and metabolic syndrome.

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A metabonomic comparison of urinary changes in Zucker and GK rats.

Zhao LC, Zhang XD, Liao SX, Gao HC, Wang HY, Lin DH.

Shanghai Institute of Materia Medica, The Chinese Academy of Sciences. Shanghai, China.

To further investigate pathogenesis and pathogenic process of type 2 diabetes mellitus (T2DM), the authors compared the urinary metabolic profiling of Zucker obese and Goto-kakizaki (GK) rats by NMR-based metabonomics. Principal component analysis (PCA) on urine samples of both models rats indicates markedly elevated levels of creatine/creatinine, dimethylamine, and acetoacetate, with concomitantly declined levels of citrate, 2-ketoglurarate, lactate, hippurate, and succinate compared with control rats, respectively. Simultaneously, compared with Zucker obese rats, the GK rats show decreased levels of trimethylamine, acetate, and choline, as well as increased levels of creatine/creatinine, acetoacetate, alanine, citrate, 2-ketoglutarate, succinate, lactate, and hippurate. This study demonstrates metabolic similarities between the two stages of T2DM, including reduced tricarboxylic acid (TCA) cycle and increased ketone bodies production. In addition, compared with Zucker obese rats, the GK rats have enhanced concentration of energy metabolites, which indicates energy metabolic changes produced in hyperglycemia stage more than in insulin resistance stage.

URL http://www.serena.unina.it/index.php/jop/article/view/3423/3724