Probiotics, critical illness, and methodologic bias.

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It has been proposed that probiotics can favorably influence the course of critically ill patients. To address this question, a limited systematic review was undertaken (MEDLINE search for articles published in English) to identify randomized, controlled trials that compared a group of critically ill patients taking probiotics with a group that did not. Ten such trials, mostly with high risks of methodologic bias, were identified. When the data were combined, the probiotics did not appear to influence mortality or duration of hospitalization. However, the recipients of the probiotics had fewer infectious episodes (absolute risk difference: -21%). This effect was seen particularly in trials employing one combination of probiotic agents (Pediococcus pentosaceus, Leuconostoc mesenteroides, Lactobacillus paracasei, Lactobacillus plantarum). Unfortunately, this effect may be overly optimistic, as methodologic shortcomings could have introduced biases into the trials. Three trials of patients with severe acute pancreatitis were not included in this primary analysis because not all of the patients were in the intensive care unit. The largest of these, and the one with the lowest risk of bias, demonstrated that probiotics increased mortality, in part because of the precipitation of ischemic bowel disease (in patients who were also receiving postpyloric enteral nutrition infusions). Probiotics also appeared to reduce the incidence of antibiotic-associated diarrhea in hospitalized patients, although these trials did not specifically focus only on those who were critically ill. In summary, it is not clear that probiotics are beneficial (and they may even be harmful) in the critically ill patient group.

Rosiglitazone attenuates the severity of sodium taurocholate-induced acute pancreatitis and pancreatitis-associated lung injury.


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In addition to the effect of regulating adipocyte differentiation and insulin sensitivity, peroxisome proliferator activated receptor-gamma (PPAR-gamma) ligands also exhibit anti-inflammatory effect. However, the mechanisms concerning how PPAR-gamma ligands affect acute pancreatitis and pancreatitis-associated lung injury have not been fully elucidated. This study investigated the effect of rosiglitazone, a PPAR-gamma ligand, on acute pancreatitis and pancreatitis-associated lung injury in the rat pancreatitis model induced by sodium taurocholate. Acute pancreatitis was induced by retrograde infusion of 5% sodium taurocholate (1 mL/kg) into the bile-pancreatic duct. Rosiglitazone (6 mg/kg) was administered via the femoral vein 30 min prior to the infusion of sodium taurocholate. The severity of pancreatitis was evaluated by serum amylase level, myeloperoxidase activity, and pathology. Pancreatitis-associated lung injury was evaluated by myeloperoxidase activity, the magnitude of pulmonary edema and pathology. Intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor-alpha mRNA expression were studied using reverse transcriptase polymerase chain reaction. ICAM-1 protein expression was studied using Western blot analysis. Prophylactic administration of rosiglitazone attenuated: 1) serum amylase level; 2) myeloperoxidase activity of pancreatic and pulmonary tissue; 3) expression of tumor necrosis factor-alpha and ICAM-1 in pancreas and lung; and 4) pancreas and lung pathological damage. The study demonstrated that rosiglitazone exerts a protective effect against sodium taurocholate-induced pancreatic and pulmonary injury.

Early versus delayed cholecystectomy in patients with biliary acute pancreatitis.

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Cholecystectomy is mandatory to prevent further biliary events in patients with biliary acute pancreatitis (AP), but timing of cholecystectomy remains a subject of ongoing debate. The objective of the present, retrospective study was to compare the outcomes of early (within 2 weeks after onset of disease) versus delayed cholecystectomy in patients with biliary AP. Between January 2000 and December 2005, 112 patients underwent cholecystectomy because of biliary AP. Thirteen patients were excluded from analysis.
because of necrotizing pancreatitis on the initial computed tomography. Thirty-two were operated within 14 days (group A) and 67 after a longer time period (group B). The primary end point of the study was the rate of biliary complications before cholecystectomy. There were no differences regarding conversion rates to open surgery (6% vs. 3%; P=0.59), local (3% vs. 4%; P=1.00), or systemic complications (0% vs. 3%; P=1.00), and mean postoperative stay (4.7 vs. 5.7 days; P=0.40). Nevertheless, a greater rate of recurrent biliary pancreatitis was found in the group undergoing cholecystectomy later (0% vs. 13%; P<0.03). The timing of cholecystectomy seems to have no clinically relevant effect on local or systemic complications, but delaying cholecystectomy is associated with an increase of biliary complications in patients with non-necrotizing biliary AP.

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Cannabinoid receptor-1 blockade attenuates acute pancreatitis in obesity by an adiponectin mediated mechanism.


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Obesity is a risk factor for increased severity of acute pancreatitis. Adipocytes produce adiponectin, an anti-inflammatory molecule that is paradoxically decreased in the setting of obesity. The authors have shown that adiponectin concentration inversely mirrors the severity of pancreatitis in obese mice. Cannabinoid receptor CB-1 blockade increases circulating adiponectin concentration. The authors, therefore, hypothesize that blockade of CB-1 would increase adiponectin and attenuate pancreatitis severity. Forty lean (C57BL/6J) and 40 obese (Lepr(Db)) mice were studied. Half of the mice in each strain received intraperitoneal injection of the CB-1 antagonist rimonabant (10 mg/kg daily for 7 days); the others received vehicle. Pancreatitis was induced by intraductal glycodeoxycholate infusion and intravenous cerulein (6 h). Daily probiotics or placebo were administered intragastrically, starting five days prior to AP. After cerulein infusion, ileal mucosa was collected for measurements of E. coli K12 and 51Cr-EDTA passage in Ussing chambers. Tight junction proteins were investigated by confocal immunofluorescence imaging. Ileal mucosal apoptosis, lipid peroxidation, and glutathione levels were determined and glutamate-cysteine-ligase activity and expression were quantified.

AP-induced barrier dysfunction was characterized by epithelial cell apoptosis and alterations of tight junction proteins (i.e. disruption of occludin and claudin-1 and up-regulation of claudin-2) and correlated with lipid peroxidation (r=0.8). Probiotic pre-treatment diminished the AP-induced increase in E. coli passage (probiotics 57.4±33.5 vs. placebo 223.7±93.7 a.u.; P<0.001), 51Cr-EDTA flux (16.7±10.1 vs. 32.1±10.0 cm/s x10^-6; P=0.005), apoptosis, lipid peroxidation (0.42±0.13 vs. 1.62±0.53 pmol MDA/mg protein; P<0.001), and prevented tight junction protein disruption. AP-induced decline in glutathione was not only prevented (14.33±1.47 vs. 8.82±1.30 nmol/mg protein, P<0.001), but probiotics even increased mucosal glutathione compared with sham rats (14.33±1.47 vs. 10.70±1.74 nmol/mg protein, P<0.001). Glutamate-cysteine-ligase activity, which is rate-limiting in glutathione biosynthesis, was enhanced in probiotic pre-treated animals (probitotics 2.88±1.21 vs. placebo 1.94±0.55 nmol/min/mg protein; P=0.05) coinciding with an increase in mRNA expression of glutamate-cysteine-ligase catalytic (GCLc) and modifier (GCLm) subunits. Probiotic pre-treatment diminished AP-induced intestinal barrier dysfunction.


Probiotics prevent intestinal barrier dysfunction in acute pancreatitis in rats via induction of ileal mucosal glutathione biosynthesis.


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Oxidative stress contributes to intestinal barrier failure during acute pancreatitis (AP). The authors studied actions of multispecies probiotics on barrier dysfunction and oxidative stress in experimental AP. Fifty-three male Sprague-Dawley rats were randomly allocated into five groups: 1) controls, non-operated; 2) sham-operated; 3) AP; 4) AP and probiotics; and 5) AP and placebo. AP was induced by intraductal glycodeoxycholate infusion and intravenous cerulein (6 h). Daily probiotics or placebo were administered intragastrically, starting five days prior to AP. After cerulein infusion, ileal mucosa was collected for measurements of E. coli K12 and 51Cr-EDTA passage in Ussing chambers. Tight junction proteins were investigated by confocal immunofluorescence imaging. Ileal mucosal apoptosis, lipid peroxidation, and glutathione levels were determined and glutamate-cysteine-ligase activity and expression were quantified. AP-induced barrier dysfunction was characterized by epithelial cell apoptosis and alterations of tight junction proteins (i.e. disruption of occludin and claudin-1 and up-regulation of claudin-2) and correlated with lipid peroxidation (r=0.8). Probiotic pre-treatment diminished the AP-induced increase in E. coli passage (probiotics 57.4±33.5 vs. placebo 223.7±93.7 a.u.; P<0.001), 51Cr-EDTA flux (16.7±10.1 vs. 32.1±10.0 cm/s x10^-6; P=0.005), apoptosis, lipid peroxidation (0.42±0.13 vs. 1.62±0.53 pmol MDA/mg protein; P<0.001), and prevented tight junction protein disruption. AP-induced decline in glutathione was not only prevented (14.33±1.47 vs. 8.82±1.30 nmol/mg protein, P<0.001), but probiotics even increased mucosal glutathione compared with sham rats (14.33±1.47 vs. 10.70±1.74 nmol/mg protein, P<0.001). Glutamate-cysteine-ligase activity, which is rate-limiting in glutathione biosynthesis, was enhanced in probiotic pre-treated animals (probitotics 2.88±1.21 vs. placebo 1.94±0.55 nmol/min/mg protein; P=0.05) coinciding with an increase in mRNA expression of glutamate-cysteine-ligase catalytic (GCLc) and modifier (GCLm) subunits. Probiotic pre-treatment diminished AP-induced intestinal barrier dysfunction.
and prevented oxidative stress via mechanisms mainly involving mucosal glutathione biosynthesis.

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**EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification.**
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EUS is increasingly used in the diagnosis of chronic pancreatitis (CP). A number of publications in this field have used different EUS terminology, features, and criteria for CP, making it difficult to reproduce their findings and apply them in clinical practice. Moreover, traditional criteria such as the Cambridge classification for CP are arguably outdated and have lost their relevance. The authors aimed to establish consensus-based criteria for EUS features of CP. Thirty-two internationally recognized endosonographers anonymously voted on terminology of EUS features, rank order, and category (major vs. minor criteria). Consensus was defined as greater than two thirds agreement among participants. Major criteria for CP were: 1) hyperechoic foci with shadowing and main pancreatic duct (PD) calculi; and 2) lobularity with honeycombing. Minor criteria for CP were cysts, dilated ducts equal to, or greater than, 3.5 mm, irregular PD contour, dilated side branches equal to, or greater than, 1 mm, hyperechoic duct wall, strands, nonshadowing hyperechoic foci, and lobularity with noncontiguous lobules. In a complex disease such as CP that has no universally accepted reference standard, an EUS-based criterion for diagnosis can be determined by expert consensus opinion and the existing body of evidence. Here the authors present the new "Rosemont criteria" for the EUS diagnosis of CP.

**Gut 2009 Feb 24.**
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**Recent advances in autoimmune pancreatitis.**
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Autoimmune pancreatitis (AIP) is distinct from calcifying and obstructive forms of chronic pancreatitis. Clinically and histologically it has two distinct subsets: a) lymphoplasmacytic sclerosing pancreatitis or Type 1 AIP which appears to be a systemic disease characterized by abundant infiltration of affected organs with IgG4 positive plasma cells; and b) duct centric or Type 2 AIP characterized by granulocyte epithelial lesions in the pancreas without systemic involvement. In AIP a marked lymphoplasmacytic infiltrate that responds dramatically to steroid therapy suggests an autoimmune etiology. However, the target autoantigen(s) and the effector cells in AIP remain speculative. Though elevated serum levels of IgG4 and a tissue infiltration with IgG4 positive plasma cells are consistently seen in Type 1 AIP, the role of IgG4 in its pathogenesis remains unknown. Recent development of animal models of AIP will help improve our understanding of the pathogenesis of these newly described forms of chronic pancreatitis.

**Virchows Arch 2009 Feb 24.**
(PMID: 19238431)

**Diagnosis of autoimmune pancreatitis by core needle biopsy: application of six microscopic criteria.**
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Autoimmune pancreatitis (AIP) has been established as a special entity of chronic pancreatitis (CP). However, its clinical distinction from pancreatic cancer and other types of CP is still difficult. The aim of this study was to evaluate the efficacy of pancreatic core needle biopsy for the diagnosis of AIP. In 44 core needle biopsy specimens, the authors assessed the following microscopic features: granulocytic epithelial lesions (GELs), more than ten IgG4-positive plasma cells/HPF, more than ten eosinophilic granulocytes/HPF, cellular fibrosis with inflammation, lymphoplasmacytic infiltration, and venulitis. All biopsies that showed four or more of the six features (22 of 44) were obtained from 21 of 26 patients whose clinical diagnosis and follow-up were consistent with AIP. All non-AIP CP patients (n=14) showed three or less than three of the features in their biopsies. GELs were only observed in biopsy specimens from AIP patients. In conclusion, these data indicate that the six criteria applied were able to recognize AIP in 76% of biopsy specimens using a cut-off level of four. When the specimens that revealed only three features but showed GELs were added, the sensitivity rose to 86%. Therefore, pancreatic core needle biopsy can make a significant contribution to the diagnosis of AIP.

**Eur Radiol 2009 Feb 24.**
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**Groove pancreatitis: a diagnostic challenge.**
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Groove pancreatitis is a distinct form of chronic pancreatitis characterized by inflammation and fibrous tissue formation, affecting the groove area between the head of the pancreas, the duodenum and the common bile duct. It is manifested on imaging by a sheet-like mass in the groove area near the minor papilla. Thickening of the duodenal wall and cystic transformation in the duodenal wall also represent common imaging features. Pathogenesis is still unclear, and clinical presentation is not specific. Endoscopic ultrasonography (EUS), computed tomography (CT) and magnetic resonance imaging (MRI) demonstrate imaging findings consistent with the disease in typical cases, but specific diagnosis is challenging in a number of patients where biopsy is required. The disease may mimic pancreatic, common bile duct or duodenal wall cancer that requires prompt and excessive surgical intervention, as opposed to groove pancreatitis where initial conservative treatment is suggested. The clinical, histopathological and radiological features on cross-sectional imaging of this entity are discussed in this review, and differential diagnostic clues are given.

Aliment Pharmacol Ther 2009 Feb 13. (PMID: 19222416)

Clinical trial: A randomized trial comparing fluoroscopy guided percutaneous technique versus endoscopic ultrasound guided technique of celiac plexus block for treatment of pain in chronic pancreatitis.


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Celiac plexus block (CPB) is a management option for pain control in chronic pancreatitis. CPB is conventionally done by percutaneous technique with fluoroscopic guidance (PCFG). Endoscopic ultrasound (EUS) is increasingly used for CPB as it offers better visualization of the plexus. There are limited data comparing the two modalities. The aim of this study was to compare the pain relief in chronic pancreatitis among patients undergoing CPB either by PCFG technique versus EUS guided technique. Chronic pancreatitis patients with abdominal pain requiring daily analgesics for more than 4 weeks were included. Fifty six consecutive patients (41 males, 15 females) participated in the study. EUSG-CPB was done in 27 and PCFG-CPB in 29 patients. In both the groups, 10 mL of bupivacaine (0.25%) and 3 mL of triamcinolone (40 mg) was given on both sides of the celiac artery through separate punctures. Pre and post procedure pain scores were obtained using a 0-10 visual analogue scale. Improvement in pain scores was seen in 70% of subjects undergoing EUS-CPB and 30% in percutaneous-block group. (P=0.044) EUS-guided celiac block appears to be better than PCFG-CPB for controlling abdominal pain in patients with chronic pancreatitis.


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Pancreatic ductal adenocarcinoma (PDA) is a lethal disease, with surgery being the only curative modality for localized disease, and gemcitabine with or without erlotinib remains the standard of therapy for unresectable or metastatic disease. CEACAM6 is overexpressed in human PDA independent of stage or grade and causes anoikis resistance when dysregulated. Because murine monoclonal antibody 13-1 possesses target-specific cytotoxicity in human PDA cell lines, the authors humanized anti-CEACAM6 single-chain variable fragment (scFv) based on monoclonal antibody 13-1. PEGylation of the glycin-serine linker was used to enhance plasma half-life. These scFvs bound CEACAM6 with high affinity, exhibited cytotoxic activity, and induced dose-dependent poly(ADP-ribose) polymerase cleavage. Murine PDA xenograft models treated with humanized scFv alone elicited tumor growth inhibition, which was enhanced in combination with gemcitabine. Immunohistochemistry showed significant apoptosis, with inhibition of angiogenesis and proliferation, and preservation of the target. Collectively, these results have important implications for the development of novel antibody-based therapies against CEACAM6 in PDA.

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Imaging pancreatic cancer using bioconjugated InP quantum dots.

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The authors report the successful use of non-cadmium-based quantum dots (QDs) as highly efficient and nontoxic optical probes for imaging live pancreatic
Semiconductor quantum dots (QDs) have traditionally been synthesized in organic phase and transferred to aqueous solution by functionalizing their surface with silica, polymers, short-chain thiol ligand, or phospholipid micelles. However, these complex steps result in: i) a reduction of the quantum yield (QY) of QDs; ii) partial degradation of the QDs; and iii) a drastic increase in the hydrodynamic size of QDs, which may hinder their biomedical applications. In this work, the fabrication and applications of cysteine-capped CdTe/ZnTe QDs, which are directly synthesized in aqueous media, as optical probes for specific targeting of pancreatic and esophageal cancer cells in vitro are reported, as well as their capability for in vivo imaging. The CdTe/ZnTe QDs are synthesized in a one-pot method and capped with amino acid cysteine, which contains both carboxyl and amine functional groups on their surfaces for bioconjugation. The fabricated QDs have an ultrasmall hydrodynamic diameter (3-5 nm), possess high QY (52%), and are non-toxic to cells at experimental dosages. Confocal imaging is used to demonstrate a receptor-mediated uptake of antibody-conjugated QDs into pancreatic cancer cells in vitro. In vitro cytotoxicity studies (MTS-assay) show that the IC(50) value of these QDs is approximately 160 microg mL⁻¹, demonstrating low toxicity. In addition, the QDs are used for small-animal imaging where the in vivo biocompatibility of these QDs and their clearance following systemic injection is studied.

(PMID: 19239583)

**Likelihood ratios of clinical, laboratory and image data of pancreatic cancer: Bayesian approach.**

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The diagnosis of pancreatic cancer (PC) is most frequently established in advanced stages. The aim of this study is to estimate the likelihood ratios (LRs) of diagnostic data with regards to PC that could be used to approach an earlier diagnosis. A case-control study of 300 patients (150 histological diagnosed cases of PC and 150 age-matched controls hospitalized for study of jaundice, abdominal pain, weight loss and/or chronic pancreatitis) was conducted. Bayesian probabilities in the form of LRs were estimated for PC predictions. Probability of PC was associated with jaundice (odds ratio, OR, 2.89; 95% confidence interval, 95% CI, 1.71-4.85), glycemic disturbance (OR 5.64; 95% CI 2.36-13.46), tobacco index >20 (OR 2.11; 95% CI 1.08-4.09) and tumour marker CA 19-9 (OR 9.33; 95% CI 1.36-63.95). Computed tomography showed the highest test performance with regards to PC when comparing with other diagnostic tests. LRs for variables relevant to PC were estimated, among the most relevant: jaundice LR+ 1.92, CA 19-9 LR+ 5.36 and computed tomography LR+ 4.15. The prediction model with an endoscopic retrograde cholangio-pancreatography at a tertiary referral hospital determined a 67% probability of detecting PC. Through a Bayesian approach we can combine clinical, laboratory and imaging data to approximate to an earlier diagnosis of PC.

(PMID: 19244227)

**Characteristic differences in cephalic arch geometry for diabetic and non-diabetic ESRD patients.**

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Fistula access in chronic haemodialysis patients is recommended. The first and second choice for location of fistula placement is radial-cephalic followed by the brachiocephalic fistula. Fistula access using the brachiocephalic fistula. Fistula access in chronic haemodialysis patients is recommended. The first and second choice for location of fistula placement is radial-cephalic followed by the brachiocephalic fistula. Fistula access using the brachiocephalic fistula. Fistula access in chronic haemodialysis patients is recommended. The first and second choice for location of fistula placement is radial-cephalic followed by the brachiocephalic fistula. Fistula access using the brachiocephalic fistula. Fistula access in chronic haemodialysis patients is recommended. The first and second choice for location of fistula placement is radial-cephalic followed by the brachiocephalic fistula. Fistula access using the brachiocephalic fistula. Fistula access in chronic haemodialysis patients is recommended. The first and second choice for location of fistula placement is radial-cephalic followed by the brachiocephalic fistula. Fistula access using the brachiocephalic fistula. Fistula access in chronic haemodialysis patients is recommended. The first and second choice for location of fistula placement is radial-cephalic followed by the brachiocephalic fistula. Fistula access using the brachiocephalic fistula. Fistula access in chronic haemodialysis patients is recommended. The first and second choice for location of fistula placement is radial-cephalic followed by the brachiocephalic fistula.
cephalic vein often results in cephalic arch stenosis that is less common in diabetics for unclear reasons. The objective of the current study is to determine if geometry of the cephalic arch differs between diabetics and non-diabetics. In a retrospective design, 57 patients with brachiocephalic fistula access had radiology films of the cephalic arch reviewed for geometric analysis. Twelve patients were excluded from final analysis because of stent placement in the cephalic arch. Measurements made included diameter of the cephalic vein, minimum radius of curvature and angle of the arch. Demographics were statistically analysed to determine the association with the geometric measurements. Global and local measurements showed evidence of two arch types. Wider arch angles and larger R/d were associated with diabetes by univariate (P<0.05) and multivariate analyses (P<0.05). A wider arch angle was also associated with a history of right permcath access by multivariable analysis (P=0.042). Based on this study, it was found that there are two distinct types of cephalic arch geometries. Patients having diabetes mellitus show a significant probability of having a larger R/d ratio and wider arch angle. This study has given insight into structural alterations in geometry of the cephalic arch of diabetics with brachiocephalic fistula access.

Cognitive function is not associated with recurrent foot ulcers in patients with diabetes mellitus and neuropathy.


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This single centre prospective study assessed the association of cognitive function and risk for ulcer relapse in 59 patients with diabetes mellitus (age 65.1 years, diabetes duration 16.5 years, HbA1c 7.4%), peripheral neuropathy and a history of foot ulceration. Premorbid and current cognitive functions were measured (multiple choice vocabulary test (Lehrl), Number-Symbol-Test, Mosaic-Test HAWIE-R and Trail-Making-Test A and B (Reitan)). Prevalence of depression was evaluated retrospectively (diagnoses in patient files, use of antidepressive medication). Patients were re-examined after 1 year. Results: 3 (5%) patients died during follow-up (1 of sepsis, 2 of heart problems). The remaining 56 patients developed 27 (48%) new foot ulcerations (21, 78%, minor lesions Wagner stadium 1). Characteristics of patients with and without ulcer relapse were not different. In binary logistic regression cognitive function is not predictive of foot re-ulceration. In conclusion, cognitive function is not an important determinant of foot re-ulceration.