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ORAL PRESENTATIONS

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1. GENERATION OF FATTY ACID CHLOROHYDRINS IN ACUTE PANCREATITIS

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Introduction: Severe acute pancreatitis causes inflammation and necrosis of adipose tissue. In this study we assessed the generation of chlorinated fatty acids in necrotic adipose tissue.

Methods: In a model of taurocholate pancreatitis in rats we analyzed the levels of fatty acid chlorohydrins in adipose tissue, ascites and plasma. Chlorohydrins were also administered into the peritoneal cavity and then peritoneal macrophages were obtained to assess activation. Finally we determined the level of chlorohydrins in plasma of patients with acute pancreatitis.

Results: We detected chlorohydrins of oleic and linoleic acids in adipose tissue and ascites. Oleic acid chlorohydrin was detected in plasma. Chlorohydrins administration induced expression of TNF-α in peritoneal macrophages. In patients with severe pancreatitis chlorohydrins levels were significantly increased.

Conclusions: During acute pancreatitis chlorinated fatty acids are generated and may enhance the inflammatory response. In patients, levels of chlorohydrin increase in patients with severe pancreatitis.

2. SECURITY AND UTILITY OF THE EUS-GUIDED INTRACYSTIC BIOPSY OF CYSTIC TUMORS OF THE PANCREAS. A NEW DIAGNOSTIC TECHNIQUE, PRELIMINARY RESULTS

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Introduction: Cystic tumors of the pancreas are a frequent finding because of the extended use of image diagnostic techniques. Although most of them are asymptomatic, some of them may be malignant. Fine Needle Aspiration (FNA) guided by EUS is associated to low sensitivity. Tissue collection from the cyst wall may improve sensitivity.

Methods: We present the preliminary results of a prospective study enrolling patients that were referred to our unit with cystic tumors of the pancreas to undergo EUS. A 19G Echo Tip ultra needle (COOK) was used. After it have been aspirated almost the half of the liquid we introduced through the needle a 220 × 0.8 mm biopsy forceps, (Polyscope, Lumenis Surgical) and obtained several pieces of tissue from the inner lining of the cyst. The biopsies were processed in formaldehyde. We determined the concentration of tumor markers in the liquid that has been aspirated. We followed up for complication immediately after the biopsy on the first 24h and 7 days after it.

Results: Number of patients 15, males 4 and females 11. Mean age 64.9 SD 9.27. Location; pancreatic head 9, body 4, tail 1, uncus 1. The mean diameter was 3.3cm SD 1.26. There were nodules in the inner lining of the cyst in 6 cases. It was technically possible to introduce the needle and make biopsies in all the cases. The FNA material was meaningful to diagnosis in 6 cases (40%) by other hand the biopsy specimen was meaningful to diagnosis in 10 cases (66.7%), the combo rate of diagnosis was 13 cases (86.7%). Intraductal Papillary Mucinous Neoplasm was diagnosed in 6 cases, Mucinous Cystadenoma in 4 and Pseudocyst in 3. The median (P25-P75) of CEA in all the cases with mucinous neoplasm was 129(46.3-225.9) and we found only two cases with CEA > 192 ng/ml. In this series, there were no complications related to the technique.

Conclusions: this new technique enables us to obtain tissue specimen from the inner lining of the cyst without an increase in the rate of complications. The possibility to obtain tissue from the inner of the cyst improves the diagnostic capability of the EUS.

3. EUS GUIDED BIOPSY IF SOLID PANCREATIC TUMORS. ACCURACY OF A NEW A DEVELOPED HISTOLOGY NEEDLES (19-GAUGE AND 22 GAUGE) COMPARED TO STANDARD CYTOLOGY NEEDLES (22-GAUGE AND 25-GAUGE)

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Introduction: Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is an accurate technique for sampling pancreatic

solid lesions. However, cytology possesses limitations to its final yield and accuracy. Nowadays new needles for EUS-FNA are available, allowing the obtention of histological samples. Aim of the study was to evaluate the accuracy of a newly developed 19-gauge and 22-gauge histology needles, compare to the standard FNA needles.

Methods: 83 consecutive patients (mean age 65.5 years, range 42-86, 47 male), who underwent EUS for the evaluation of solid pancreatic masses were prospectively included in the study. EUS were performed using a convex array echoendoscope (Pentax EG-3870UTK), connected to an ultrasound equipment (Hitachi). Biopsies were performed with the new developed 19-gauge and 22-gauge histology needles (Echotip®Procore™, Cook Medical Inc, Limerick Ireland). FNA were performed with the standard 22-gauge and 25-gauge needles (Echotip®UHDF, Cook Medical Inc, Limerick Ireland). With histology needles, sample obtained was recovered into ThinPrep® and processed for histological analysis, after one pass. With standard cytology needles, samples were recovered into slides and fixed for cytological evaluation, following standard methodology. Results were compared to the gold standard of surgical histopathology, or global clinical and radiological assessment and follow-up in non-operated cases. Results are shown as mean ± SD or percentage (95%CI), and compared by chi-square test. Diagnostic accuracy was also evaluated.

Results: Size of solid pancreatic masses was 41.5 ± 19.8 mm. 50 tumors were located in the head of the pancreas, 29 in the body, and 4 in the tail. After randomization, 38 punctures (45.8%) were performed with histology needles (21 with 19-gauge and 17 with 22-gauge), and 45 (54.2%) with standard cytology needles (25 with 25-gauge and 20 with 22-gauge). In 36 cases diagnosis proved to be correct with histology needles (94.7%) (16/17 with 22-gauge, and 20/21 with 19-gauge), while with the standard needles diagnosis proved to be correct in 36 cases (80.0%) (15/20 with 22-gauge, and 21/25 with 25-gauge) (p = 0.046). There were no complications.

Conclusions: Performing a EUS-guided biopsy with the new developed histology needles is more accurate than with the standard cytology needles, allowing to obtain histological samples in all cases after only one pass.

4. STUDY OF THE LUNG INJURY DEVELOPMENT IN AN ANIMAL MODEL OF ACUTE PANCREATITIS

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Introduction: Acute pancreatitis (AP) represents a fundamental clinical problem with increasing incidence. The most important mortality predictor is the development of multiple organ failure and the commonest affected organ is the lung.

Objectives: To study the reason why acute pancreatitis develops lung injury.

Methods: AP was induced by intraductal infusion of 5% sodium taurocholate in rats. One group of these animals were injected intraperitoneally with sodium cromoglycate 30 minutes before AP induction. Another group were infused intravenously by pancreatic trypsin. We evaluated the pancreas and lung inflammation and the expression of protease activated receptor type 2 (PAR-2) in different types of mast cells and macrophages.

Results: Mast cell degranulation was observed in pancreas during pancreatitis but not changes were observed in lung. Macrophages and mast cells express PAR-2. Animals with AP have increased the amount of trypsin in plasma. Injection of this trypsin in healthy animals increases the inflammation in lungs. In addition, this trypsin also activates mast cells and macrophages in vitro and increases the density of PAR-2 in the membrane of these cells.

Conclusions: Pancreatic mast cells play an important role in triggering the local and systemic inflammatory response in the early stages of acute pancreatitis. Lung mast cells are not involved in the inflammatory response to pancreatic damage, almost in acute pancreatitis of three hours of evolution. The trypsin generated during the AP could be responsible of the lung damage development through the activation of PAR-2 in different cell types.

5. CONTRAST-ENHANCED HARMONIC EUS WITH A SECOND GENERATION CONTRAST AGENT (SONOVUE®) IN THE DIFFERENTIAL DIAGNOSIS OF SOLID PANCREATIC TUMORS

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Introduction: Despite recent advances in imaging techniques, differential diagnosis of solid pancreatic tumors remains a challenge. The use of ultrasound (US) contrast agents, which allows evaluating tumoral microvascularization in real time, has supposed an advance in this setting. Nowadays, second-generation US contrast agents produce harmonic signals at lower acoustic powers being more suitable for endoscopic ultrasound (EUS) imaging at low acoustic powers. Aim of the present study was to evaluate the accuracy of determining the microcirculation pattern by contrast-enhances harmonic EUS (CEH-EUS) with a second generation contrast agents in the differential diagnosis of solid pancreatic tumors.

Methods: 37 consecutive patients (mean age 62 years, range 32-89, 25 male), who underwent a EUS for the evaluation of a solid pancreatic mass were prospectively included. EUS and CEH-EUS were performed with linear Pentax-EUS and Hitachi-Preirus. Once the solid pancreatic lesion was identify, microvascularization was evaluated in real time by CEH-EUS using the same quantity of the contrast agent (4.8 ml of Sonovue® e.v.) and a low mechanical index, during 2 minutes. Final diagnosis was based on surgical histopathology and/or EUS-guided biopsy and global clinical and radiological assessment and follow-up in non-operated cases. Data are shown as mean (± SD). Diagnostic accuracy was calculated by drawing the corresponding ROC curves.

Results: Size of masses was 36.7 ± 19.1 mm. Tumors were located in the head (n = 27), body (n = 9) and tail (n = 1) of the pancreas. Final diagnosis was pancreatic adenocarcinoma (n = 24), neuroendocrine tumor (NET) (n = 3), inflammatory mass (n = 7), pancreatic metastasis (n = 1), mucinous cistoadenoma (n = 1), and autoimmune pancreatitis (n = 1). According to CEH-EUS evaluation, 25 lesions presented a hypoenhanced pattern (22 pancreatic adenocarcinoma, 1 mucinous cistoadenoma, 1 inflammatory mass, and 1 pancreatic metastasis), 6 lesions an isoenhanced pattern 5 inflammatory masses and the case of autoimmune pancreatitis), and 5 lesions a hyperenhanced pattern. The sensitivity, specificity and accuracy of a hypoenhanced pattern for diagnosing PA were 92%, 84.6%, and 89.5%, respectively (AUC = 0.883).

Conclusions: CEH-EUS with Sonovue® is a very useful tool for the differential diagnosis of solid pancreatic tumors. A hypoenhanced patters is highly specific for pancreatic adenocarcinoma.

6. EARLY PREDICTION OF INCREASED FLUID REQUIREMENTS IN ACUTE PANCREATITIS

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Introduction: Early prediction of fluid requirements in patients with acute pancreatitis (AP) would be useful to tailor fluid therapy. Thus, undesirable effects of an insufficient or excessive fluid volume would be avoided.

Objectives: To investigate early predictors of increased fluid requirements and to develop a score to optimize fluid management.

Methods: Retrospective analysis of a prospective cohort study. Four hundred and twenty-two adult patients with AP were randomly divided into a derivation cohort (n = 219) and a validation cohort (n = 203). The main outcome variable, Increased Fluid Requirements (IFR), was defined in both cohorts as those patients who were administered a fluid volume higher than 75th percentile within the first 48h. Predictive ability of IFR was studied from 20 variables obtained at the emergency department.

Results: Variables most strongly associated with IFR in the derivation cohort were: Glucose > 160 mg/dL, Age < 70, Hematocrit > 44% and Leukocyte count > 14,000/mm^3. Fluid Resuscitation Score (FRESCO) was designed by assigning a point to every variable. Predictive ability of IFR in the FRESCO score was similar for both the derivation [Area under the Receiver Operating Curve (AUC) 0.764 (0.687-0.840)] and the validation [AUC 0.727 (0.648-0.806)] cohorts. FRESCO has been shown to be a reliable predictor of fluid sequestration in the validation cohort [AUC 0.706 (0.610-0.801)].

Conclusions: The best predictive variables of increased fluid requirements in patients with acute pancreatitis are glucose, hematocrit, age, and leukocyte count. We have described and validated a predictive score for fluid requirements in acute pancreatitis.

7. DOES TOBACCO INDUCE INTRACELLULAR TRYPSINOGEN ACTIVATION AND ACINAR CELL NECROSIS? A DOSE-DEPENDENT IN-VITRO STUDY COMPARED TO ALCOHOL

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Introduction: Premature intracellular activation of zymogens within the acinar cells is the main early event in chronic pancreatitis (CP), leading to autodigestion and necrosis. Tobacco, besides alcohol, is a toxic risk factor for CP, but whether it is able to activate intracellular trypsinogen and to induce acinar cell necrosis is unknown.

Objectives: To analyze the effect of different concentrations of tobacco compared to different concentrations of alcohol in the intracellular activation of trypsinogen and induction of acinar cell necrosis.

Methods: Pancreatic acinar cells were isolated from Swiss mouse pancreas by enzymatic degradation (collagenase) and mechanic degradation, filtration and centrifugation. Intracellular trypsin activity and acinar cell necrosis in response to six different concentrations of tobacco (from 0.001 to 0.5 mg/ml) and alcohol (from 10 to 100 mM) were measured at 20 minute-intervals for one hour by fluorescence assay. CCK at supramaximal dose (10^{-7}M) was used as positive control. Data were analyzed by Anova-test.

Results: Trypsinogen was significantly activated by 0.4 mg/ml of tobacco ($p < 0.005$), but not by alcohol. Tobacco at 0.4 and 0.5 mg/ml induced 13% and 14% cell necrosis, respectively, after 40 minutes ($p < 0.05$ compared to negative control), similar to that obtained by supramaximal dose of CCK, however, alcohol induced no significant cell necrosis. Percentage of necrosis increases linearly with the concentration of tobacco ($r = 0.92$, $p = 0.04$).

Conclusions: Tobacco at a dose of 0.4mg/ml but not alcohol stimulates the intracellular activation of trypsin. Tobacco, but not alcohol, induces cellular necrosis.

8. ZEB1 AND ZEB2 MEDIATE PANCREATIC FIBROBAST INDUCED EPITHELIAL-TO MESENCHYMAL TRANSITION (EMT) IN PANCREATIC CANCER

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Introduction: EMT renders neoplastic cancer cells the ability to migrate and to invade distant organs. AIMS: To analyze the effect of pancreatic fibroblasts (PF) on inducing EMT in pancreatic cancer cells and to identify the trasncription factors (Snail, Slug, ZEB1, ZEB2) that mediate EMT process.

Methods: Human PFs were isolated from pancreatic specimens obtained from unaffected margins of pancreatic adenocarcinoma, serous cistoadenoma, and from chronic pancreatitis. PF were cultured until complete cellular activation, as assessed by expression of α-smooth muscle actin, vimentin and fibronectin. Human pancreatic cancer cells Panc-1 were exposed to PF conditioned medium and EMT analyzed by cell morphology, migration, and E-cadherin expression (quantitative RT-PCR and immunoblot). Gene expression of Snail, Slug, ZEB1, and ZEB2 was analyzed by quantitative RT-PCR, and their activity modulated by RNAi.

Results: Conditioned media from all types of activated PFs induced EMT changes in Panc-1 cells, as shown by morphological transition from cobblestone shaped to fibroblast-like cells, stimulation of cell migration, and E-cadherin down-regulation; mRNA expression of Snail and Slug was greatly enhanced by PF; ZEB1 expression increased at the protein but not at the mRNA level, suggesting that PF promote ZEB stability. Combined RNA downregulation of ZEB1 and ZEB2, but not of Snail and/or Slug, suppressed E-cadherin repression induced by PF.

Conclusions: Activated PFs promote the invasive phenotype of pancreatic cancer cells through ZEB1 and ZEB2 activation.

9. ABNORMALITIES IN THE EXOCRINE PANCREAS MAY EXPLAIN POOR GLYCEMIC CONTROL IN TYPE 2 DIABETES: A PILOT CASE-CONTROL STUDY

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Introduction: Type 2 diabetes is a highly prevalent disease. On the contrary, chronic pancreatitis (CP) is considered as an underdiagnosed disease. Diabetes secondary to undiagnosed CP

could be thus misdiagnosed as type 2 diabetes. Since glycemia in diabetes secondary to CP is difficult to control, we aim at evaluating morphological changes of CP in relation to glycemic control in type 2 diabetic patients.

Methods: A prospective case-control pilot study was designed. Consecutive compliant patients with type 2 diabetes and poor glycemic control (HbA1C > 7%) despite optimal antidiabetic therapy were included as cases. Morphologic evaluation of the pancreas was performed by endoscopic ultrasound (EUS) (linear Pentax EG 3870UTK and Hitachi Preirus) under conscious sedation. Parenchymatous and ductal EUS criteria of CP were evaluated. Pancreatic fibrosis was quantified by EUS-elastography in the head, body and tail of the pancreas, and the mean value considered as the result. Type 2 diabetics with adequate glycemic control and undergoing upper EUS for any extrapancreatic reason were included as controls. Written informed consent was obtained before EUS after explaining the study. Data are shown as mean ± SD and range, and compared by the Student t test.

Results: A total of 10 patients (mean age 59.8 years, range 42-70 years, 6 female) and 10 controls (mean age 65.3 years, range 46-79 years, 8 female) have been included in this pilot study. HbA1C was 9.4 ± 1.6% in patients and 6.0 ± 0.4% in controls ($p = 0.001$). Time of diabetes was of 16.8 years (range 3-37 years) in patients and 9.6 years (range 5-15 years) in controls ($p = 0.08$). Eight cases (80%) and none of the controls had changes of chronic pancreatitis at EUS (mean number of EUS criteria 3.6, range 3-5). Stiffness of pancreatic tissue as a sign of fibrosis was higher in cases than in controls (strain ratio 3.6 ± 1.1 vs 1.9 ± 0.2, respectively; $p < 0.001$). Pancreatic atrophy was much more frequent in cases than in controls, and the diameter of the pancreas at the body level was 9.7 ± 2.8 mm in cases vs 14.7 ± 1.2 mm in controls; $p < 0.001$).

Conclusions: Type 2 diabetic patients with poor glycemic control frequently present with morphological changes of the pancreas defined by pancreatic atrophy, fibrosis and EUS signs of chronic pancreatitis. An abnormal digestion in these cases, together with abnormal secretion of pancreatic hormones involved in glucose homeostasis, may explain a poor glycemic control in these patients. Whether pancreatic enzyme substitution therapy may help to improve glycemic control in these patients deserves further investigations.

10. PRIMARY ACINAR CELL CULTURE: IS CELL VIABILITY ENOUGH FOR RESEARCH OF PANCREATIC PATHOPHYSIOLOGIC EVENTS?

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Introduction: Dispersed pancreatic acinar cells and tumoral acinar cell lines are, nowadays, the main in vitro models for research of pancreatic pathophysiology. Primary acinar cell culture would be an essential tool for the studies of pathophysiologic events, like early chronic pancreatitis events. Aim: To evaluate the number and viability of acinar cells, its morphology and enzyme activity on primary culture.

Methods: Pancreatic tissue was obtained from male Swiss mice, 4-6 weeks. Acinar cells were isolated by enzymatic and mechanical dissociation tissue, filtration and centrifugation. Viability was analyzed with trypan blue exclusion. Acinar cells were cultured in complete medium DMEM Hams 12, fetal bovine serum 15% and streptomycin-penicillin, in 100 mm culture dishes. 24 hours later, medium was changed to remove dead cells. Morphology evaluation and amylase activity were assessed at 24 hours intervals. Morphological changes and proliferation of acinar and stellate cells was evaluated by inverted and confocal microscopy. Amylase activity was measured by colorimetric method and expressed as percentage of amylase.

Results: 7 experiments were performed. Mean of acinar cells number was 4.12×10^4 cells/ml and viability was of 77 per cent. In the second day, viable acinar cells were attached to the bottom of the plate, amylase secretion increased fourfold and amylase activity was maintained through the days. Intracelular amylase decreases 60 per cent of the initial concentration in day five. From day 5 to 8, stellate cells were activated in periacinar areas, but not in other region of the dishes. From the ninth day, acinar cells start the senescence, losing their morphology, and stellate cells proliferate to reach a confluence of 90 per cent.

Conclusions: Acinar cells are viable up to 9 days in primary culture and intracellular amylase concentration was maintained up to day 5, so this could be a good model for the study of the early pancreatic physiopathogenic events. Factors secreted by acinar cells in culture could play a role in stellate cells activation.

11. ASSOCIATION OF FAT CONSUMPTION WITH CLINICAL MANIFESTATIONS, DIAGNOSIS AND SEVERITY OF CHRONIC PANCREATITIS

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Introduction: A high fat diet leads to pancreatic hyperstimulation and could cause earlier onset of clinical manifestations of chronic pancreatitis (CP) and thus lead to an earlier diagnosis of the disease.

Objectives: To evaluate the effect of the total amount of dietary fat and of fat in different food groups (dairy, meat, fish, ready meals, vegetables and legumes, fruits, bread and cereals, sweets) on the age of diagnosis of CP, and clinical, morphological and functional severity of the disease at diagnosis.

Methods: Prospective cohort study where patients diagnosed of CP were consecutively recruited. Morphological and functional severity at diagnosis was evaluated by endoscopic ultrasound (7 or more EUS criteria of the disease and presence of calcifications) and 13_MTG breath test (presence or absence of exocrine pancreatic insufficiency –EPI-), respectively. Dietary habits before diagnosis were quantified by fulfilling a detailed nutritional questionnaire. A consumption of fat higher than 30% of daily calories intake was considered as excessive according to the recommendations of the Spanish Society of Nutrition. Results are shown as OR and 95% CI. Statistical analysis was performed by ANOVA test, T-student and logistic regression.

Results: 168 patients were included (128 men, mean age 47 years, range 17-76). 58.9% smoked, 57.5% drank. 42.5% had continuous abdominal pain and 29.9% had chronic diarrhea. 22.4% of the patients presented EPI at diagnosis and 23% suffered from a morphologically severe CP. 14.3% of patients had an excess of fat consumption. Excess of dietary fat increased the risk of continuous abdominal pain (OR = 2.55 (1.034 to 6.308), $p = 0.042$), and decreased the age of diagnosis (37.1 ± 13.9 years vs 45.8 ± 13.1 years; $p = 0.003$). Fat consumption, either total or in different food groups, was not associated to morphological or functional severity of the disease at diagnosis. Toxic consumption increased the risk of EPI development (OR 2.273 (1.030-5.016); $p = 0.042$) and severe morphological CP (OR = 3.151 (1.159-8.572); $p = 0.025$) regardless of fat intake.

Conclusions: A high fat diet increases the risk of continuous abdominal pain leading to an earlier diagnosis of CP. Fat intake plays no role on the morphological or functional severity of CP at diagnosis.

12. ASSESSMENT OF SALIVARY ELECTROLYTES IN CHRONIC PANCREATITIS

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Introduction: CFTR partly governs salivary and pancreatic secretion. CFTR dysfunction, as in Cystic Fibrosis (CF), leads to pancreatic atrophy and fibrosis. Factors associated with chronic pancreatitis (smoking, alcohol and autoimmunity) may alter CFTR function, and some pancreatitis patients carry CFTR gene mutations.

Objectives: To assess electrolytes in sweat and saliva in patients with proven chronic pancreatitis.

Methods: Basal and stimulated salivary secretion was collected protected from air-CO_2 contamination from 34 non-smoking healthy subjects, 28 Cystic Fibrosis and 50 chronic pancreatitis. Bicarbonate, pH, chloride, sodium and osmolarity were determined. A sweat tests was performed. Patients were studied for CFTR gene mutations (DGGE-direct sequencing).

Results: Chronic pancreatitis patients had higher chloride concentration in sweat than healthy controls (43.3 ± 2.3 vs 30.2 ± 2.1 mEq/L; $p < 0.0003$), but less than CF patients (102.8 ± 6.1). Salivary pH (6.71 ± 0.05) and bicarbonate (5.5 ± 0.5 mEq/L) were lower than controls (7.05 ± 0.04 and 8.9 ± 0.6), but patients had higher chloride concentration (42.5 ± 3 vs 24.3 ± 0.7 mEq/L) and osmolarity (110 ± 7.3 vs 76.6 ± 2.6 mOsm/L). CF patients had similar values as chronic pancreatitis patients. CFTR gene mutations were identified in 33% of chronic pancreatitis and in 100% of CF patients. In chronic pancreatitis sweat and salivary electrolytes were independent of the presence of CFTR mutations. CF patients with pancreatic insufficiency had higher chloride concentration both in sweat and in saliva.

Conclusions: Sweat and salivary electrolyte abnormalities suggest global CFTR dysfunction in patients with chronic pancreatitis that may have pathophysiological implications.