IMPACT OF EXOCRINE PANCREATIC INSUFFICIENCY ASSOCIATED WITH ACUTE PANCREATITIS AND PANCREATIC ENZYME REPLACEMENT THERAPY ON GUT MICROBIOTA, IMMUNOLOGICAL CHANGES AND QUALITY OF LIFE

INFORMED CONSENT

MARCH 17TH, 2021

Impact of exocrine pancreatic insufficiency associated with acute pancreatitis and pancreatic enzyme replacement therapy on gut microbiota, immunological changes and quality of life

A longitudinal prospective study and blind randomized placebo-controlled clinical trial

Short title: Exocrine pancreatic insufficiency after acute pancreatitis and pancreatic enzyme replacement therapy

Keywords
Acute pancreatitis
Pancreatic exocrine insufficiency
Gut microbiota
Immunology

Abstract
Introduction: Acute pancreatitis represents an acute inflammatory process of the pancreas, which undergoes local and systemic complications, associated with non-negligible morbidity and mortality, and significant economic and quality of life impact. Even after the recovery phase, the development and persistence of sequelae from the inflammatory/necrotic process, including exocrine and endocrine pancreatic insufficiencies, are frequent. Although well documented as consequence of other pancreatic conditions, exocrine pancreatic insufficiency (EPI) after acute pancreatitis is poorly studied and probably underdiagnosed. The prevalence, diagnosis, independent risk factors and therapeutic approaches for EPI after acute pancreatitis need further investigation. Recent evidence suggests the involvement of the pancreas-intestinal axis and immunological dysfunction in several pancreatic pathologies, although their role in the development of EPI after acute pancreatitis is still scarce. Pancreatic enzyme replacement therapy (PERT) is the only treatment currently available in EPI, but the timing for start and duration of this therapy in acute pancreatitis remain to be established.
Objectives: Primary objectives: To determine the prevalence, clinical, analytical and nutritional biomarkers and duration of EPI after acute pancreatitis, as well as changes in gut microbiota and immunologic response, and quality of life in EPI and response to PERT after acute pancreatitis. Secondary objectives: To determine the prevalence and biomarkers associated with endocrine pancreatic insufficiency following acute pancreatitis and the presence of gut dysbiosis and immunologic changes in acute pancreatitis according to its severity.
Methods: Prospective longitudinal study of total of patients consecutively admitted to the gastroenterology Department of Coimbra Hospital and University Centre with acute pancreatitis diagnosis and double-blind randomized placebo-controlled clinical trial of PERT in patients developing EPI after acute pancreatitis. This study will be conducted in 4 Phases: Phase 1 - Recruitment of patients with acute pancreatitis and stratification of them according to the severity of acute pancreatitis and development of EPI (12-month follow-up), diagnosed by fecal elastase-1, 13C-labeled mixed triglyceride breath test assessing exocrine pancreatic function and comparison of them with 72-hour fecal fat quantification, as gold standard; Phase 2 – Double-blind randomized placebo-controlled trial in patients with EPI after acute pancreatitis for PERT with assessment of efficacy and safety of this therapy
at 1 and 6 months post-randomization; Phase 3 - Evaluation of richness, diversity and uniformity of gut microbiota by DNA sequencing using the hypervariable region of the 16S ribosomal RNA gene as a taxonomic identification marker and assessment of quality of life using SF-36 and QLC-C30-V.3 scales (validated versions for the Portuguese population) in EPI patients after acute pancreatitis, and the impact of PERT on clinical course, gut dysbiosis and quality of life of patients (at the diagnosis of acute pancreatitis, EPI and after PERT); and Phase 4 – Analysis of immunological changes through the study of cell populations by flow cytometry (CD4+, CD8+, B-cell, T-cell, natural killer cells, cells ratio) and cytokines, chemokines and growth factors by xMAP/Luminex, at the diagnosis of acute pancreatitis, EPI and after PERT.
Expected results, impact and scientific outputs: Data on the prevalence of EPI after acute pancreatitis in its different forms of severity and the role of gut dysbiosis and immunologic changes remains unclear. It's expected that an adequate and timely diagnosis of this clinical condition will allow an early start of therapy with positive impact on clinical course, immunologic and gut homeostasis, survival and quality of life. With this study we expect to obtain a prevalence of EPI at admission of 25-62%, which should decrease during

followup. Alcoholic etiology, severity of acute pancreatitis and the presence of pancreatic necrosis should be positively associated with the presence of EPI after acute pancreatitis. The prevalence of endocrine pancreatic insufficiency (pre-diabetes or diabetes mellitus) should be up to 40%. Nutritional deficits (single or multiple), breath test assessing exocrine pancreatic function and fecal elastase-1 are also expected to be positively associated with the development of EPI. It's expected that patients with acute pancreatitis developing EPI will have significant changes on gut microbiota and immunologic response, and PERT and/or gut microbiota modulating therapy, including prebiotics, probiotics, symbiotics and fecal microbiota transplantation, and probably targeted immunotherapies may have a beneficial impact on all patients or groups at risk, such as EPI, severe or necrotizing acute pancreatitis by reverting gut and immunologic dysbiosis, and improving quality of life.

Literature review

Acute pancreatitis, an acute inflammatory process of the pancreas, is associated with significant mortality and morbidity.1-3 It can lead to local and systemic complications related to the inflammatory/necrotic process, including exocrine pancreatic insufficiency (EPI) and endocrine pancreatic insufficiency (diabetes mellitus), recurrent pancreatitis and chronic pancreatitis. These complications can arise and/or persist even after hospital discharge.4-8 The main manifestation of EPI is weight loss secondary to malnutrition due to micronutrient, fat-soluble vitamin and lipoprotein deficiencies.5,6,9 Although EPI is well established in the context of chronic pancreatitis, pancreatic cancer and pancreatectomy, its occurrence in the background of acute pancreatitis remains unknown and probably underdiagnosed.5 Data on the prevalence of EPI following acute pancreatitis are scarce and controversial, ranging from 20 to 71%.3,5,6 Some studies list alcohol etiology, the severity of acute pancreatitis and the presence of pancreatic necrosis as risk factors associated with EPI.5,6 However, the knowledge in this area is equally scarce and uncertain. Acute pancreatitis complications, including EPI, can lead to a significant economic impact and impaired quality of life.5,6,10

In clinical practice, there is no a universally easy and reliable test for the diagnosis of EPI.5,6,11,12 Gold standard diagnosis implies direct tests or 72-hour fecal fat quantification. However, their clinical applicability is limited. Valid alternatives such as fecal elastase-1 and 13C-labeled mixed triglyceride breath test assessing exocrine pancreatic function have gained special interest and wide use for their availability, cost and ease of application.12 Based on fecal elastase-1, EPI has been reported at 26.5%, 26.1% and 9.4% for a follow-up of <12months, 12-36months and >36months, respectively.5,6 Recent evidence suggests an increasing importance of the pancreas-intestinal axis in pancreatic pathology given the central role of the pancreas in controlling metabolism via its exocrine and endocrine pancreatic functions, possibly due to bacterial metabolites as short-chain fatty acids, immune modulation and pancreatic excretion of antimicrobials. Changes in gut microbiota have been more documented for pancreatic cancer and type 1 diabetes mellitus.13,14 Recently, [ZhHeLiCaHuLi19] showed that severe acute pancreatitis can also course with gut dysbiosis by decreased Firmicutes and Bacteroidetes and increased Protobacteria.15 However, the presence and implications of gut dysbiosis associated with acute pancreatitis and EPI following acute pancreatitis increasing risk of gut-derived infection, remains unclear. In recent years, efforts have been dedicated to find early predictors, alone or in association, of severity, organ dysfunction, and development of complications in patients with acute pancreatitis. In fact, our study group has also been dedicating itself to this thematic, having carried out studies and reflections with publications in international and national journals, identifying C-reactive protein (CRP),16,17 red cell distribution width (RDW) and RDW to total serum calcium ratio,7 as main early predictors (at admission of patients and within the first 24 hours of hospitalization) of severity in acute pancreatitis. However, no single biomarker or score demonstrated high accuracy in early prediction of severity or prognosis of acute pancreatitis to be used in clinical practice7,16,17 and, additionally, there are no studies on early predictors in the development of the EPI complication after acute

pancreatitis. Important immunological changes, which may become biomarkers, have been described as associated with severe acute pancreatitis, such as interleukin(IL)-6, IL-8, IL- 10 and CRP. Recent studies have shown that IL-6 ≥28.90pg/mL in the first 48 hours (sensitivity:62.9%; specificity:80.0%), and the growth differentiation factor(GDF)-15 >3183.36pg/mL (sensitivity:89.5%; specificity:76.9%), pentraxin(PTX)-3 >1.05pg/mL (sensitivity:85.0%; specificity:88.0%) and hepatocyte growth factor(HGF) >3020.1pg/mL (sensitivity:60.0%; specificity:92.8%) at admission were good predictors of severity in acute pancreatitis.18-20 However, there are no data on the main immunological changes associated with the development of EPI following acute pancreatitis. Pancreatic enzyme replacement therapy (PERT), the only treatment currently available for EPI secondary to other causes than acute pancreatitis, has benefit in EPI

secondary to chronic pancreatitis,21 post-pancreatic surgery6,22,23 and non-resectable pancreatic cancer.24 However, its use in EPI following acute pancreatitis lacks clinical evidence, needs further studies and its routine application in clinical practice is currently not recommended.5,6 Some studies have been shown improvement in survival of patients with EPI
secondary to severe or necrotizing acute pancreatitis and patients undergoing necrosectomy.23,25 When to start PERT and for how long to obtain clinical and nutritional benefits and
the reversal of gut dysbiosis and immunologic changes in EPI following acute pancreatitis remain to be elucidated. Future prospective studies addressing these key issues are indispensable to determine the prevalence of EPI following an acute pancreatitis event and its predictors, as well as a
double blind randomized placebo-controlled trial to assess the impact, efficacy and safety of PERT and its repercussions on gut microbiota, immunological status, clinical and nutritional course and patients' quality of life. In the future, new therapeutic targets may be explored in EPI following acute pancreatitis, such as manipulation of gut microbiota including prebiotics, probiotics, symbiotics and perhaps fecal microbiota transplantation and probably targeted immunotherapies. PERT and these new therapies could be applied to all patients after acute pancreatitis or in high-risk groups, including EPI.

Plan and methods

A. Study hypothesis

The authors hypothesize that exocrine pancreatic insufficiency (EPI) is a frequent and underdiagnosed complication of acute pancreatitis. Homeostasis of gut microbiota and immunological status are significantly altered in acute pancreatitis, mainly due to its severity and EPI development with important implications in clinical and nutritional course and quality of life. Pancreatic enzyme replacement therapy (PERT) and eventually new therapies modulating gut microbiota and targeted immunotherapies may reverse gut dysbiosis and immunological changes with impact on acute pancreatitis clinical course and improve quality of life.

B. Objectives

Primary objectives

- To determine the prevalence and duration of EPI following acute pancreatitis, and analytical and nutritional biomarkers related to the development of this complication;
- To evaluate when to start, the efficacy, safety and the duration of PERT in patients with EPI following acute pancreatitis;
- To assess changes in gut microbiota in EPI following acute pancreatitis and response to PERT;
- To assess changes in immunologic response in EPI following acute pancreatitis and response to PERT;
- To assess quality of life in EPI following acute pancreatitis and response to PERT.

Secondary objectives

- To determine the prevalence and biomarkers associated with the development of endocrine pancreatic insufficiency following acute pancreatitis (type 3 diabetes mellitus, including
new-onset pre-diabetes and/or diabetes mellitus);
- To evaluate changes in gut microbiota according to acute pancreatitis severity;
- To evaluate immunological changes according to acute pancreatitis severity.

C. Expected results, study clinical impact and scientific outputs

Data on the prevalence and biomarkers of EPI after acute pancreatitis in its different forms of severity and the role of gut dysbiosis and immunologic changes remains unclear. An adequate and timely diagnosis of this clinical condition will allow an early start of therapy with positive impact on clinical course, immunological and gut homeostasis, survival and quality of life. Therefore, a study on the prevalence and biomarkers of EPI in patients with acute pancreatitis, a randomized placebo-controlled trial to determine the timing for start and duration of PERT in EPI and the implications of PERT on gut microbiota and immunological response is urgently needed.

EPI is expected to be a frequent complication of acute pancreatitis, which is likely to increase with acute pancreatitis severity, with significant changes on gut microbiota and immunologic response and an impaired quality of life. Results of this study may have important clinical implications in clinical practice regarding changes in gut microbiota and immunological status, and clinical and nutritional implications of EPI following acute pancreatitis; when to start and for how long PERT should be applied and repercussions of this therapy in clinical course, reverting gut dysbiosis and immunological changes, and improving

quality of life; and the possible benefit of additional unexplored therapies such as gut microbiota modulating therapy including probiotics, prebiotics, symbiotics, fecal microbiota transplantation and targeted immunotherapies. These therapies could have a positive impact in all patients or high-risk group of patients with acute pancreatitis including EPI.

D. Methodology and Stages of project development

D.1. Type of study

Unicentric longitudinal prospective study. Regarding the evaluation of gut microbiota and immunological changes, the study will also be blind, as the researcher responsible for sequencing and immunological analyses will not know patients' EPI status. For evaluation the response to PERT in patients with acute pancreatitis and EPI, the study will be doubleblind (for the patient who will not know which therapy he will be taking (PERT/placebo) and for the researchers responsible for sequencing and immunological analyses) randomized placebo-controlled clinical trial. The trial will be registered on the https://clinicaltrials.gov platform.

D.2. Study population

Patients with the first episode of acute pancreatitis

D.3. Study design

This project will take place in 4 distinct phases:

Phase 1: Recruitment of patients with acute pancreatitis and stratification of them according to the severity of acute pancreatitis and development of EPI (12-month follow-up).

All patients admitted to the Gastroenterology Department of Coimbra Hospital and University Centre by the first episode of acute pancreatitis will be included, consecutively, according to the revised Atlanta criteria 20124 and taking into account the inclusion/exclusion criteria and the minimum number of patients needed to obtain statistical power.

Inclusion criteria: Definitive diagnosis of acute pancreatitis, according to revised Atlanta criteria 2012.4

Exclusion criteria: Age <18years; History of allergy, hypersensitivity or contraindication to use of PERT; Prior acute pancreatitis; Other causes that may occur with EPI, including celiac disease, diabetic gastroparesis, chronic pancreatitis, cystic fibrosis, pancreatic neoplasia, ampuloma, somatostatinoma, somatostatin analog therapy, small bowel pathology, inflammatory bowel disease, and rare diseases associated with exocrine pancreatic insufficiency (Zollinger-Ellison syndrome, Shwachman-Diamond syndrome, Johanson-Blizzard syndrome); Prior gastrointestinal or pancreatic surgery or endoscopic/surgical therapy for obesity; medication with orlistat or acarbose; Respiratory pathology (severe chronic obstructive pulmonary disease), hepatic (Child-Pugh C cirrhosis) or biliary (obstructive jaundice) severe pathology; Non-compliance for PERT (when indicated); Uncontrolled thyroid pathology; Refusal/incapacity to give informed consent; and Follow-up period <12months after acute pancreatitis diagnosis.

Sample size calculation: For an estimated prevalence of EPI in the adult population of 25% and a drop-out rate of 10%, it was determined that for a 95% confidence level and 10% sampling error, it will be necessary to include 42 patients in each of the therapeutic arms (PERT vs placebo), making a total of 84 patients.

Diagnosis of EPI and stratification of patients: See Task 1.

Phase 2: Double-blind randomized placebo-controlled trial for patients with EPI after acute pancreatitis for PERT and collection of stool and blood samples before and after PERT/placebo (6 months post-randomization).

Randomization of patients with EPI following acute pancreatitis for PERT vs placebo. The efficacy, safety and compliance of PERT will be evaluated at 1 (for adjusting PERT dose) and 6 months after PERT start.

Phase 3: Analysis of gut microbiota and assessment of quality of life, and the impact of PERT on clinical and nutritional course, gut dysbiosis and patients' quality of life (at the diagnosis of acute pancreatitis, EPI and after PERT). Evaluation of richness, diversity and uniformity of gut microbiota by DNA sequencing

using the hypervariable region of the 16S rRNA gene. Assessment of quality of life using validated Portuguese versions of SF-36 and QLC-C30-V.3 Assess of PERT impact on clinical and nutritional course, gut dysbiosis and patients' quality of life.

Phase 4: Analysis of immunological changes and the impact of PERT on clinical and nutritional course and immunological status (at the diagnosis of acute pancreatitis, EPI and after PERT). Evaluation of immunological changes through the study of cell populations by flow cytometry (CD4+, CD8+, B-cell, T-cell, natural killer cells, cells ratio) and cytokines, chemokines and growth factors by xMAP/Luminex. Assess PERT impact on clinical and nutritional course and immunological changes.

D.4. Statistical analysis

Using of Statistical Package for the Social Sciences (SPSS) version 25.0 (IL, USA). The statistical significance level will be for a p-value < 0.05. The distribution of data normality will be evaluated by Kolmogorov-Smirnov or Shapiro-Wilk tests. Continuous variables will be expressed as mean and standard deviation or median and interquartile range. Categorical variables will be expressed as frequency and percentage. Univariable analysis will be performed using the Kruskal-Wallis test or Anova test (continuous variables) and Qui-squared test test (categorical variables). The Wilcoxon or Friedman test and the t-Student or Anova test will be used to compare paired data. Cox regression multivariable analysis will be used to determine the independent factors associated with exocrine and endocrine pancreatic insufficiencies. Analysis of PERT efficacy will be performed per-Protocol (PP), excluding
loss of follow-up and PERT non-compliance. The temporal evaluation of EPI and PERT response will be evaluated through Kaplan-Meier survival curves. The genome sequences will be grouped in OTU according to their similarity. The alpha taxonomic richness and diversity of stool samples will be expressed in observed species and Shannon index. The composition of fecal microbiota will be expressed in rarefaction curves and comparison of the differences in OTU richness with the t-Welch test. Immunological findings will be expressed by radar charts and representative FACS dot-plots. Additional statistical analysis will be defined a posteriori.

D.5. Ethical aspects

The project will be subject to the standards of good clinical practice and will at all times comply with the ethical precepts in the World Medical Association Helsinki's Declaration and updates, including the Oviedo agreement. This study was approved by Ethical Committee of University of Coimbra (Ref n.º CE-169/2019). Written informed consent will be obtained from all patients. The confidentiality of the data will be respected at all times, by means of the anonymity of the data in the database, in accordance with the General Data Protection (UE 2016/679) and updates.

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