# Reducing disease progression after acute pancreatitis

## PhD Thesis

Doctoral School of Pharmacologycal and Pharmaceutical Sciences, Medical School,
University of Pécs, Pécs
Head: Erika Pintér, MD, PhD, DSc



**Márk Félix Juhász, MD**
*Institute for Translational Medicine, Medical School, University of Pécs, Pécs*
*Heim Pál National Pediatric Institute, Budapest*

Supervisor:
**Andrea Párniczky, MD, PhD**
*Institute for Translational Medicine, Medical School, University of Pécs, Pécs*
*Heim Pál National Pediatric Institute, Budapest*
*Center for Translational Medicine, Semmelweis University, Budapest*

Program Director:
**Péter Hegyi, MD, PhD, DSc, MAE**
*Institute for Translational Medicine, Medical School, University of Pécs, Pécs*
*Institute of Pancreatic Diseases, Semmelweis University, Budapest*
*Center for Translational Medicine, Semmelweis University, Budapest*

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## I. Scientific metrics

| | |
|---|---|
| Number of publications **related to the subject** of the thesis: | 3 (3 first author) |
| Cumulative impact factor of publications related to the thesis: | 14.777 |
| D1: -, Q1: 3, Q2: -, Q3: -, Q4: - | |
| Number of **total accepted/published** articles: | 17 (5 first author) |
| Cumulative impact factor of the published articles: | 66.707 |
| D1: 3, Q1: 13, Q2: 1, Q3: -, Q4: - | |
| Number of total citations according to **MTM2:** | 68 independent |
| https://m2.mtmt.hu/gui2/?type=authors&mode=browse&sel=10070611&view=dataSheet | |
| Hirsch Index: 4 | |
| Number of total citations according to Google Scholar | 139 |
| https://scholar.google.com/citations?view_op=list_works&hl=en&hl=en&user=fxRkqtMAAAAJ | |
| Hirsch Index: 6 | |

## II. Publications related to the subject of the thesis

**Juhász MF**, Ocskay K, Kiss S, Hegyi P, Párniczky A. Insufficient etiological workup of COVID-19-associated acute pancreatitis: A systematic review. **World J Gastroenterol**. 2020 Oct 28;26(40):6270-6278. doi: 10.3748/wjg.v26.i40.6270. PMID: 33177799; PMCID: PMC7596641.
**Q1, IF: 5.742**

**Juhász MF**, Farkas N, Szentesi A, Wedrychowicz A, Nita AF, Lásztity N, Tészás A, Tokodi I, Vincze Á, Eross B, Izbéki F, Czakó L, Papp M, Hegyi P, Párniczky A. Pancreatic family history does not predict disease progression but connotes alcohol consumption in adolescents and young adults with acute pancreatitis: Analysis of an international cohort of 2,335 patients. **Front Med** (Lausanne). 2022 Sep 12;9:801592. doi: 10.3389/fmed.2022.801592. PMID: 36172540; PMCID: PMC9511134.
**Q1, 5.058**

**Juhász MF**, Vereczkei Z, Ocskay K, Szakó L, Farkas N, Szakács Z, Zádori N, Wilschanski M, Pandol SJ, Joly F, Capurso G, Arcidiacono PG, Izbéki F, Czakó L, Papp M, Czopf L, Hegyi P, Párniczky A. The EFFect of dietary fat content on the recurrence of pancreaTitis (EFFORT): Protocol of a multicenter randomized controlled trial. **Pancreatology**. 2022 Jan;22(1):51-57. doi: 10.1016/j.pan.2021.10.002. Epub 2021 Oct 14. PMID: 34750077.
**Q1, IF: 3.977**

## III. Introduction

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas, most commonly elicited by gallstones and alcohol. It is one of the most common, potentially dangerous reasons behind abdominal pain in the adult emergency department. While most cases are mild, without complications, 10-30% will develop moderate or severe disease resulting in longer hospitalization, local or systemic complications and an up to 40% mortality. But after the acute episode, disease progression can be observed – around the third of patients will experience recurrent episodes (ARP), 10-20% will develop chronic pancreatitis (CP).

Determining the etiology of AP has an important role in the management – while the general therapeutic approach is the same, etiology-specific interventions might be necessary during hospitalization and eliminating the risk factor is essential for avoiding recurrent episodes. However, etiological workup is often lacking: biliary AP can be assumed based on a finding of bile stones in the gallbladder, alcohol can be implicated in case of any consumption, but perhaps most problematic is the work-up of proposed "idiopathic" cases. In a cohort analysis of around 2,400 AP cases by Zádori et al. serum triglyceride measurement was performed in only 28% of the presumed idiopathic cases, additional imaging investigations occur only in 5% and 13% at the time of the first and the second "idiopathic" AP.

Etiological investigation is crucially important, as the correct knowledge and removal of risk factors is the best possible way to avoid disease progression. In that regard, genetics and indicative family history of pancreatic disease also play an important role, as they can pose a continuous risk for pancreatitis formation. Regardless, the current guidelines do not recommend genetic testing among adult patients with AP, so out of a research context, genetic factors will mostly remain unexplored. Family history can indicate genetic risk, but its prognostic role is unclear in adults with AP and other factors (such as alcohol consumption, smoking, obesity, diabetes, etc.) can be in the background – this question is yet unexplored.

Regardless of our current efforts, 10-30% of all patients with AP will develop ARP. A meta-analysis of 14 observational studies found a 10% prevalence of CP in patients with a single episode of AP, and 36% in patients with at least 1 recurrence. Aside from the elimination of known risk factors (cholecystectomy, alcohol and smoking cessation) no interventions exist to stop or delay this progression towards CP. A possibility for idiopathic AP patients is to comply with a low-fat diet. Although this intervention is frequently recommended in a clinical context, it is not included in any of the available guidelines, and the scarce evidence comes mainly from observational studies, no randomized controlled trials (RCTs) are available.

## IV. Objectives

In our work, we used three distinct clinical scientific methodologies, with the focus of delaying disease progression towards ARP and CP, via exploring the significance of a family history of pancreatic diseases, highlighting the importance of etiological workup and designing interventions for patients with idiopathic AP to delay progression.

- We conducted a **prospective, international cohort analysis of AP patients**, to explore reasons behind a family history of pancreatic diseases and to establish how this relates with disease progression.
- We conducted a **systematic review** of case reports of AP patients where SARS-CoV-2 infection was implicated as an etiological factor. None of these case reports conducted a thorough etiological workup and they were methodologically flawed.
- We designed and initiated a **RCT** to test the benefits of a low-fat diet after idiopathic AP. In case it proves beneficial in reducing progression towards ARP and CP, it would be the first available intervention in idiopathic cases.

# V. The studies

## V.1. Pancreatic family history doesn't predict disease progression, but connotes alcohol consumption in adolescents and young adults with acute pancreatitis: Analysis of an international cohort of 2,335 patients.

### V.1.1. Introduction

In idiopathic AP, there is a higher possibility of inherited genetic alterations in the background, posing a constant and unamendable risk factor, thus increasing the likelihood of and speeding up progression towards ARP, CP and pancreatic cancer (PC). Guidelines recommend that after a second idiopathic AP episode, children should go through genetic testing, and adults should receive genetic counseling (not necessarily testing). So genetic background is often established late and often missed altogether – especially in adults or when other etiologies are present. There is however an easily assessable factor that could point towards genetic predisposition, and be useful in such cases: positive pancreatic family history.

In pediatric AP, a family history of AP and CP is strongly associated with earlier ARP and CP onset. Adult CP guidelines also strongly recommend assessment, however, we failed to identify any clinical studies examining the connection between ARP, CP and pancreatic family history. Even though assessing family history is uncomplicated, examining it poses two major points of importance: observing whether it is a risk factor for disease progression in adults; and mapping associations with possible explanatory factors, to reach a greater understanding of AP, ARP and CP.

Our aim was to examine associations between pancreatic family history, ARP and CP rate, idiopathic etiology, and risk factors of AP in different pediatric and adult age groups.

### V.1.2. Methods

#### V.1.2.1. Study design, data collection, participants

This study is a secondary analysis of the international, multicenter, prospective AP registry maintained by the Hungarian Pancreatic Study Group (HPSG). Between 2012 and 2019, 2,559 episodes of AP were enrolled in the registry. A rigorous, four-tier quality control system was applied to ensure the accuracy of these data.

Both adult and pediatric AP patients with available data on the presence/absence of pancreatic family history – including AP, CP, ARP, autoimmune pancreatitis (AIP), PC – were included in our analyses (2,335 patients, with 2,470 prospectively collected episodes of AP). We compared patients with a negative pancreatic family history to patients with a positive pancreatic family history for: AP, CP, ARP, AIP or PC. To observe age-specific changes in our observed variables, we divided the cohort into age-based subgroups (see Figure 1a).

#### V.1.2.2. Variables, statistical analysis

Complications and severity of AP were determined according to the revised Atlanta criteria. While the prospective data collection period only covers eight years, a detailed personal medical history was taken, especially regarding pancreatic disease.

In case of categorical variables, we calculated event number and percentage of total, and mean and standard deviation (SD) for continuous data. Chi-squared or Fisher exact tests were applied

for categorical, the Student t-test for normally distributed continuous and Mann-Whitney U-test for non-normally distributed continuous variables, with an alpha value of 5%.

### V.1.2.3. Ethical approval, study reporting

The Scientific and Research Ethics Committee of the Medical Research Council granted the ethical approval for this registry in 2012 (22254–1/2012/EKU). The institution's human research committee approved the protocol for the registry before initiating participant enrolment. We are in compliance with the Declaration of Helsinki, reaffirmed in 2013. All patients provided their written, informed consent in case of participation.
This study was reported according to the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) statement.

## V.1.3. Results

### V.1.3.1. Participants

A total of 2,335 patients were analyzed, of which 196 (8.4%) had a positive pancreatic family history. These patients were younger (49.2±20.4 vs. 55.6±18.2 years, $p<0.001$) at the time of their first enrolment in our registry, and idiopathic AP etiology was more common (26.0% vs. 19.5%; $p=0.030$). Mild disease course occurred significantly more often in case of the first registered AP episode (78.6% vs. 71.2%; $p=0.027$), and any prospectively collected episode belonging to positive pancreatic family history group as well. The total number of episodes / person (accounting not only for registry enrolments but also episodes in medical history) was significantly higher in the positive pancreatic family history group (1.74±1.86 vs. 1.48±1.29; $p=0.010$).

### IV.1.3.2. Pancreatic family history and ARP, CP

Figure 1a shows the rate of ARP and CP (developed later or already diagnosed) with or without pancreatic family history categorized by the age of the index involvement in the AP registry. Higher rate of ARP was noted in childhood, even more so in the positive than the negative family history groups, but without statistical significance. Overall, a significantly higher rate of ARP and/or CP was found in the positive family history group (33.7% vs 25.9%, $p=0.018$).

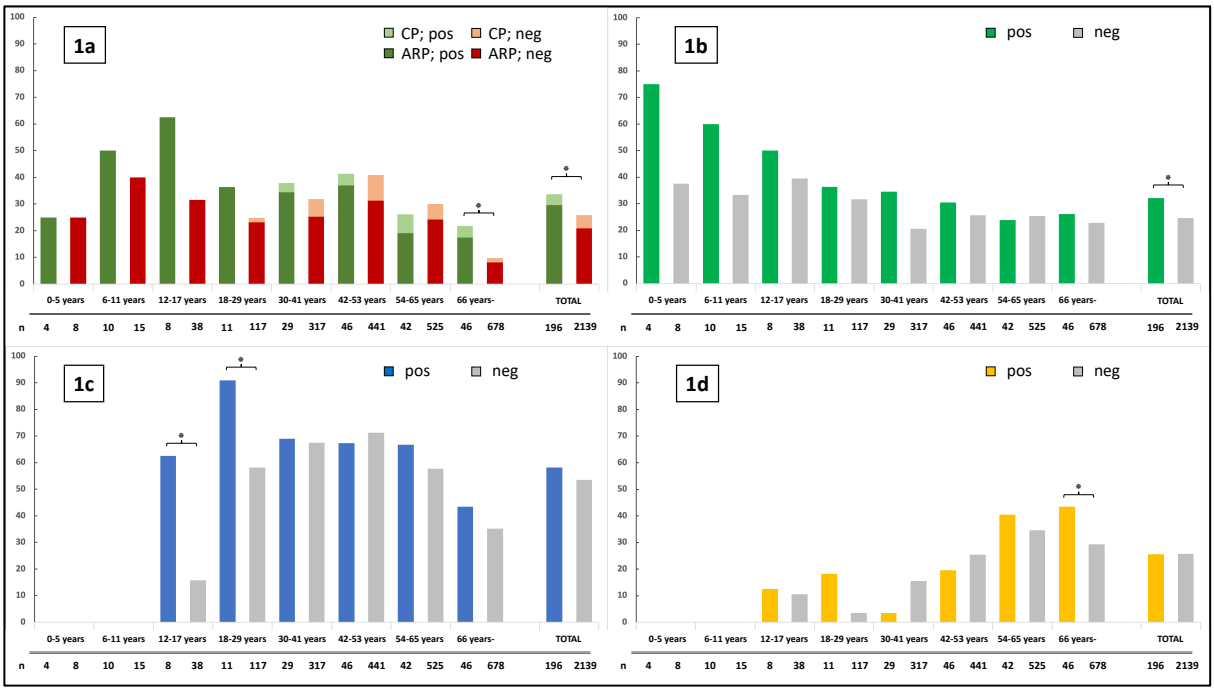


**Figure 1:** (1a): Rate of acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) in different age groups of acute pancreatitis (AP) patients with positive and negative pancreatic family history; (1b): rate of idiopathic etiology at time of the index AP registry enrolment; (1c): rate of current alcohol consumption and/or smoking at the time of the index AP registry enrolment; (1d): rate of diabetes and/or hyperlipidemia at the time of the index AP registry enrolment. Star sign indicates statistically significant difference between positive and negative pancreatic family history groups (<0.05). n: total number of participants with data on the examined variable; CP: chronic pancreatitis; ARP: acute recurrent pancreatitis; pos: positive pancreatic family history group; neg: negative pancreatic family history group.

### V.1.3.3. Association with idiopathic etiology, alcohol, smoking and metabolic factors

Among patients with a negative pancreatic family history, the rate of idiopathic episodes was higher in children (30-40%) than in adults (20-30%). We found an excess of idiopathic etiology in children with a positive family history (75% 0-5 years, 60% 6-11 years) which decreased over time to meet the negative group. Statistically significant difference was found overall (32.1% vs 24.6% in the positive vs negative groups, respectively, p=0.020) (Figure 1b).

We found a significantly higher rate of current alcohol consumption and/or smoking at the index case in the positive family history group in ages: 12-17 years (62.5% vs 15.8%, p=0.013), 18-29 years (90.9% vs 58.1%, p=0.049) but not overall (58.2% vs 53.4%, p=0.204). In the remaining age groups, balanced distribution was found (Figure 1c).

Significant difference between positive and negative family history groups regarding the presence of DM and/or hyperlipidemia at the time of the index case was observed only in patients 66 years old or above (43.5% vs 29.4% respectively, p=0.044) but not overall (25.5% vs 25.7%, p=0.950), nor in any other age subgroup (Figure 1d).

### V.1.4. Discussion

Overall, we found a significantly higher rate of ARP or CP in the positive family history group. In the age-based subgroups we observed a consistently higher rate of ARP or CP in the positive groups, but without statistical significance. Further increasing the sample size of adult subgroups – while it could lead to significant results – would likely still be a clinically irrelevant

difference. In our opinion, family history should not be used as a prognostic factor for recurrence and CP among adults.
While the negative family history group had a rate of idiopathic etiology consistently in the 20-40% range, the positive group had an excess of idiopathic AP in the pediatric age groups: peaking at 75% at 0-5 years then steadily decreasing to meet the negative group in adulthood. This is likely due to genetic risk factors being responsible for familial aggregation among pediatric patients, especially in early childhood. Next to the decline of differences in idiopathic etiology, another factor emerged at 12-17 years: we found a significantly higher rate of alcohol consumption and/or smoking in patients with a positive pancreatic family history, in this and the 18-29 years subgroup. The most likely explanation is the well-documented association between parental and offspring alcohol consumption. Regarding DM and hyperlipidemia, metabolic risk factors for AP, we found low prevalence in pediatric patients, with a gradual transition towards adulthood. Contrary to our expectations (genetic and learned behavioral components that could lead to accumulation in the family), we only saw a statistically significant difference between groups above 66 years, with a tendency starting to show in the 54-65 years subgroup.

#### V.1.4.1. Implications

This was the first cohort study to examine the ARP and CP prognostic role of family history in adults. Positive family history most likely signifies genetic background in early childhood. During adolescence and early adulthood, alcohol consumption and smoking emerges – clinicians should be aware of the significant association with pancreatic family history (probably due to harmful consumption in the family) and consider targeted intervention in such cases. Our analysis revealed that contrary to current viewpoints positive pancreatic family history is not a prognostic factor for ARP and CP in adults, so it should not be used as such.

## V.2. Insufficient etiological workup of COVID-19 associated acute pancreatitis: A systematic mini-review

### V.2.1. Introduction

Viral infections such as mumps, Coxsackie, hepatitis and herpes viruses are known causes of pancreatitis. There is a strong possibility that, like other, less common causes of AP, infectious etiology is underdiagnosed on account of insufficient workup of idiopathic cases and cases where an apparent cause (e.g. alcohol consumption) is already established.

On the other hand, during a pandemic such as with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), polymerase chain reaction (PCR) testing is made widely available. This will of course lead to a proportion of patients with a variety of diseases, including AP, being diagnosed with SARS-CoV-2 infection. Given the right temporal association, even a more experienced practitioner could be led to ponder a cause-effect relationship between coronavirus disease 2019 (COVID-19) and AP. Even more so, taking into account the often-neglected etiological workup of idiopathic cases and the opportunity to aid the scientific and medical communities by providing information on presumed complications of the infection.

This systematic review aims to assess all publications containing COVID-19 AP cases and to determine the plausibility of an association between the two.

### V.2.2. Methods

#### V.2.2.1. Protocol and registration, study eligibility

This systematic review was registered with PROSPERO as “Pancreas involvement in COVID-19: A systematic review” under registration number CRD42020186426. Any study, regardless of design, was considered eligible if it contained the original data on at least 1 SARS-CoV-2-infected individual diagnosed with AP.

#### V.2.2.2. Systematic search and selection; data extraction; risk of bias; analysis

Using the same search key as detailed in the supplementary material, the systematic search was conducted in five databases: Embase, MEDLINE (via PubMed), CENTRAL, Web of Science and Scopus. The last systematic search was carried out on 14 May 2020. The search was restricted to 2020, and no other filters were applied. Study selection and data extraction was performed as recommended by the Cochrane Collaboration. The Joanna Briggs Institute Critical Appraisal Checklist for Case Reports was used to assess risk of bias in case reports, and the Newcastle–Ottawa Scale was used for cohorts. Only qualitative synthesis was performed; no statistical analysis was carried out.

### V.2.3. Results

#### V.2.3.1. Characteristics of included studies

In total, six case reports and two retrospective cohort studies were included in this systematic review. Information on the diagnostic criteria and etiological factors of AP was collected from the appropriate case reports in Table 1. Of the six cases, five fulfilled the diagnostic criteria for AP, and in one case enzyme elevation reached the threshold, abdominal pain could not be reported on account of the patient being ventilated and sedated, and no imaging findings were disclosed.

In a retrospective cohort of COVID-19 mortality cases by Li et al., AP is listed as an underlying disease in a single patient without further clarification as to whether it is a past event from the patient's medical history or it occurred during COVID-19-related hospitalization. Hossain et al. noted three cases of AP among 119 patients presenting to the ER with non-respiratory symptoms who turned out to have concomitant SARS-CoV-2 infection.

| Author (country) | Diagnostic workup | | | COVID-19 (PCR) | Etiological workup | | | | | | | | | Quality of case reports | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Abdominal pain | Enzyme elevation (3x) | Imaging | | Biliary | Alcohol | HTG (>11.5 mmol/L) | Drug | Hyper-calcemia | Ischemia | Auto-immunity | Viral (except nCoV) | Anatomy | JBI rating ( /8) | Written as CARE |
| Aloysius et al. (USA) | + | + | - | + | ? | - | - | - | ? | ? | ? | ? | - | 3 | no |
| Anand et al. (UK) | + | ? | + | + | ? | - | ? | + | ? | ? | ? | ? | - | 0 | no |
| Hadi et al. (Denmark) | ? | + | + | + | ? | - | - | ? | - | + | ? | ? | ? | 4 | no |
| | + | + | ? | + | ? | ? | ? | + | - | + | ? | ? | ? | 2 | |
| Meireles et al. (Portugal) | + | + | - | + | ? | - | - | - | - | - | - | - | - | 1 | no |
| Morrison et al. (USA) | ? | + | ? | + | ? | ? | + | + | ? | + | ? | ? | ? | 1 | no |

**Table 1. Diagnostic and etiological workup and quality assessment of the studies.** The Atlanta criteria were used for diagnosis. Biliary microlithiasis was included in the "biliary" etiology, so an EUS or MRCP was needed to rule out this factor. Ischemia was considered in the case of shock and vasopressor therapy and was ruled out by angio-CT. Anatomical malformations were ruled out by CT. The two columns on the right demonstrate the quality of included case reports based on risk of bias according to the overall Joanna Briggs Institute (JBI) Critical Appraisal score and adherence to Case Report (CARE) guidelines on reporting cases.

### V.2.4. Discussion

The cause-effect relationship between SARS-CoV-2 and AP has not been investigated directly so far. Before regarding a new virus as a causative agent in cases where no apparent etiological factors are present, other, less frequent causes of AP must be considered.

For instance, drugs used in treating COVID-19 or comorbid conditions may cause pancreatic damage directly or indirectly. The patient presented by Anand et al. was receiving doxycycline, a drug with a documented probable association with AP. Hypertriglyceridemia, another established etiological factor frequently neglected, can also occur as a consequence of therapy, as in the case described by Morrison et al. Not only tocilizumab, but propofol and ritonavir could also have been responsible for the elevation of serum triglyceride levels in this case. In the case reports by Aloysius et al. and Meireles et al., further imaging investigations (such as endoscopic ultrasonography (EUS)) were not conducted in the proposed idiopathic cases.

Issues regarding diagnosis were also observed. Two studies not included in this review labeled patients with serum amylase and/or lipase values higher than the upper limit of normal to possess “pancreatic injury”, while only three-fold elevation can be considered a diagnostic criteria, other conditions (renal impairment, diabetes mellitus, gastroenteritis, acidosis, etc.) can lead to slight elevations in serum amylase and/or lipase that should not be regarded as an indicator of pancreatic damage. The case reports in our review carry considerable risk of bias and their deviation from the CARE guideline on reporting methods. As demonstrated, the etiological workup of patients was incomplete, and often COVID-19 was named as the causative agent of AP, while other established factors were also present.

To conclude, we strongly emphasize the need for guideline adherence when diagnosing and uncovering the underlying etiological factors of AP, even during a pandemic. As specific therapeutic options are available depending on etiology, neglecting these steps can hinder direct therapy and lower the chances of recovery, while increasing the probability of complications and recurrent episodes.

**V.2.4.1. Implications…**

…for practice: Appropriate diagnostic and etiological workup of AP is strongly recommended and bears therapeutic consequences.

…for research: Higher-quality clinical data supported by basic science findings are required to evaluate a possible causative association between SARS-CoV-2 and AP.

…for editors: The demand for the fast dissociation of knowledge should not lower the quality of research published in scientific journals.

## V.3. The EFFect Of dietary fat content on the Recurrence of pancreaTitis (EFFORT): protocol of a multicenter randomized controlled trial

### V.3.1. Introduction

While interventions exist to avoid recurrences in the case of the two major etiologies – abstinence in alcoholic AP and cholecystectomy in biliary AP – there are no preventive therapeutic options for patients with idiopathic ARP. One possibility would be to comply with a low-fat diet, which is widely recommended to AP patients, regardless of etiology. Though it is indeed frequently recommended, maintaining a low-fat diet after AP is not included in any of the guidelines and evidence is scarce. Basic science experiments and cohort studies offer conflicting results. No RCTs are available examining this question.

Our aim was to conduct a RCT comparing two low-fat diets that contain the same amount of calories and protein but have different fat contents (15 and 30% respectively) in order to determine the effect of dietary fat content reduction on AP recurrence. We wanted to include patients with idiopathic ARP as this is the group without a preventive therapeutic option. Our hypothesis is that while patients on both arms will benefit from receiving nutritional guidance, those with less fat in their diet will see an additional benefit due to the further reduction in serum lipids.

### V.3.2. Methods, design

#### V.3.2.1. Trial design, eligibility criteria

This study will be a multicenter, prospective, parallel-group RCT with a superiority framework. Participants will be randomly assigned in a 1:1 ratio to one of 2 different dietary interventions which are as follows: (1) a 'reduced fat diet' in which the daily calorie intake will be composed of 15% fat, 65% carbohydrates, 20% proteins; (2) a 'standard healthy diet' (which also qualifies as a low-fat diet and is largely based on WHO recommendations) in which the daily calorie intake will be composed of 30% fat, 50% carbohydrates and 20% proteins. Diets will be individualized to the daily calorie needs of the participant. Consultations will take place in an outpatient setting. When assigned to an intervention, first, patients will complete a food frequency questionnaire (FFQ), then receive recommendations according to the assigned group. Patients will be advised their allocated intervention in case they (1) withdraws their consent, (2) fail to attend two consecutive visits (3) develop one of the conditions mentioned in the exclusion criteria, or (4) complete the study.

Inclusion criteria: (1) individuals with at least two episodes of acute pancreatitis in the 2 years preceding the inclusion with (2) the last episode being idiopathic, who are (3) at least 14 years old.

Exclusion criteria: (1) individuals already receiving regular nutritional guidance; (2) critical condition or in terminal stage of cancer (with an expected survival <2 years); (3) undergoing treatment for active malignancy; (4) cholecystolithiasis; (5) uncontrolled diabetes mellitus; (6) pregnant or nursing; (7) body mass index <18.5; (8) regularly receiving systemic corticosteroids; (9) alcohol consumption >5 units per day or 15 units per week for men; 4 units per day or 8 units per week for women.

### V.3.2.2. Outcomes

The primary outcome measure for this trial will be (1) a composite endpoint: the recurrence of AP (given as a rate of event) AND/OR all-cause mortality.

Secondary outcome measures will be the following: (1) Pancreas-specific mortality; (2) cardiovascular cause mortality, (3) newly diagnosed CP, (4) changes in BMI, serum lipid parameters, including: (5) total cholesterol, (6) triglyceride, (7) HDL-cholesterol and (8) LDL-cholesterol; (9) serum albumin, levels of (10-13) vitamins A, D, E and K; (14) blood pressure. We will also assess (15) smoking, (16) adherence to dietary recommendations; (17) adverse events, (18) quality of life and (19) muscle strength using a handgrip dynamometer. A retrospective chart review will also be conducted at the index visit, collecting data on: comorbidities, socioeconomic status and past pancreatic history.

At enrollment and every visit, basic laboratory tests from blood will be carried out and participants will provide blood for storage in the biobank.

| STUDY PERIOD | Screening | Allocation | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Close-out |
|---|---|---|---|---|---|---|---|
| | -4 – 0 weeks | 0 week | 3 months | 6 months | 12 months | 18 months | 24 months |
| ENROLMENT: | | | | | | | |
| Eligibility screen | X | | | | | | |
| Informed consent | X | | | | | | |
| Allocation | | X | | | | | |
| INTERVENTIONS (dietary consultation) | | | | | | | |
| Reduced-fat group | | X | X | X | X | X | |
| WHO-diet group | | X | X | X | X | X | |
| ASSESSMENTS: | | | | | | | |
| Physical examination | X | X | X | X | X | X | X |
| BP, HR measurement | | X | X | X | X | X | X |
| BMI measurement | X | X | X | X | X | X | X |
| Laboratory testing | X | X | X | X | X | X | X |
| Handgrip test | | X | X | X | X | X | X |
| Food Frequency Questionnaire | | X | X | X | X | X | X |
| Quality of life | | X | X | X | X | X | X |
| Comorbidities, socioeconomic status, pancreatic history | | X | | | | | |

**Table 2 – SPIRIT schedule outlining timing of interventions and assessments.** WHO: World Health Organization; BP: blood pressure; HR: heart rate; BMI: body mass index. This figure is the author's own work.

### V.3.2.3. Sample size, recruitment

As there are no similar studies to date, we will employ a two-stage trial design – we estimated a likely accurate participant number of 384 accounting for drop-outs, equally allocated (192-192) to both intervention groups which we will refine according to the results of an interim analysis performed at the time of reaching 50% (n=192) of the planned participant number.

Recruitment will be performed in 2 distinct ways: (1) patients can be asked to participate during their pancreatitis-associated hospital stay, or (2) eligible patients identified through medical database search can be contacted with a proposal of participation.

Upon reaching 10% of the target sample size an interim safety analysis will be performed wherein the Safety Monitoring Board will review data of the patients and determine whether

the occurrence of any negative effects can be linked to any of the interventions and if needed the given intervention or the trial will be terminated for the safety of the patients.

#### V.3.2.4. Ethics, dissemination

This trial is registered on clinicaltrials.gov (NCT04761523).
This study was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (40304-11/2020/EÜIG), on 2020.08.17.
Planned start of patient recruitment: 2021.07.01.
Anticipated study duration: 5-6 years.
Study results will be published in an international scientific journal. Study sponsors have no role in writing the publication, deciding to publish and choosing the target journal.

### V.3.3. Discussion

It has been a long-standing conviction that dietary fat content, even in the absence of immoderate calorie intake and putting biliary factors aside, can influence pancreatic pathogenesis. This study is the first to test this hypothesis in a randomized, controlled setting.
The results of our study will determine the effect of modifying the dietary fat content on AP recurrence, mortality, serum lipids and weight loss in idiopathic ARP cases i.e. the patient group in which there is a dire need for interventions to positively influence the course and progression of the disease.

## VI. Summary of thesis work

The thesis and the included work ultimately focuses on avoiding or delaying the progression of AP towards ARP and CP, by examining and highlighting appropriate etiological work-up, the role of family history and initiating a RCT to see whether reducing dietary fat content can reduce AP recurrence. We used three different clinical scientific methodologies, which were, in the presented order: cohort analysis, systematic review and RCT. The main clinical implications of these works are: the novel observation of the association between family history and alcohol consumption or smoking in young adults with AP; underlining the importance of etiological workup and guideline adherence; and based on the results of the EFFORT study, establishing whether dietary fat reduction should be recommended after AP to avoid recurrences.

## VII. Conclusions and novel findings

**Pancreatic family history doesn't predict disease progression, but connotes alcohol consumption in adolescents and young adults with acute pancreatitis: Analysis of an international cohort of 2,335 patients**

- We conducted the first cohort analysis comparing AP patients with versus without a family history of pancreatic disease. We also explored the possible explanatory factors of familial aggregation.
- We found that contrary to current viewpoints positive pancreatic family history is not a prognostic factor for ARP and CP in adults, so it should not be regarded that way.
- Regarding the reasons of familial aggregation:
    - Positive family history most likely signifies genetic background in early childhood.
    - Among adolescents and young adults with a family history of pancreatic disease, alcohol consumption and smoking are prevalent – clinicians should be aware and turn to intervention in such cases.
    - We found no apparent association between family history and diabetes or hyperlipidemia.

**Insufficient etiological workup of COVID-19 associated acute pancreatitis: A systematic mini-review**

- We conducted the first systematic review of clinical reports of patients with a confirmed SARS-CoV-2 infection and AP.
- All of the included case reports failed to conduct a thorough etiological investigation. We were able to identify other possible causes in most. We also noted a high risk of bias in these papers.
- With our review we aimed to highlight a central issue in the management of AP: the lack of guideline adherence in terms of diagnostic and especially etiological workup.

**The EFFect Of dietary fat content on the Recurrence of pancreaTitis (EFFORT): protocol of a multicenter randomized controlled trial**

- We designed and launched the first RCT examining the role of dietary fat reduction after AP – this is often recommended for patients in order to avoid recurrences, although without sufficient evidence.
- The study will follow-up idiopathic patients for 2 years, collecting clinical and laboratory data.
- In case dietary fat reduction is effective, this will be the first known intervention, if not, unnecessary restriction can be avoided in the future.

## VIII. Author's contributions

In all three included articles, the author played the main role in the conceptualization of the work, planning and performing of analyses, making of the tables and figures and writing of the manuscript.

Pancreatic family history doesn't predict disease progression, but connotes alcohol consumption in adolescents and young adults with acute pancreatitis: Analysis of an international cohort of 2,335 patients

The author took part in the patient enrolment and clinical data clinical data collection from AP patients into the HPSG AP registry as well as the quality control of entered data, conceptualization of the work, curation of data tables, data analysis, making figures and tables, writing of the manuscript.

Insufficient etiological workup of COVID-19 associated acute pancreatitis: A systematic mini-review

The author took part in the conceptualization and registering of the review, designing the search key, performing the systematic search and selection, data collection from the included papers, risk of bias analysis, preparation of figures and tables, writing of the manuscript.

The EFFect Of dietary fat content on the Recurrence of pancreaTitis (EFFORT): protocol of a multicenter randomized controlled trial

The author took part in the conceptualization of the study and protocol, registry of the study, communication with participant prospect and international board members to improve design, preparation of tables and figures, preparation of questionnaires, submission for ethical approval, communicating with future centers, writing of the protocol, preparation of questionnaires. The study finally launched in the summer of 2022, 10 participants are enrolled so far.