Early and/or immediately full caloric diet versus standard refeeding in mild acute pancreatitis: A randomized open-label trial

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ABSTRACT
Refeeding after acute pancreatitis (AP) is traditionally started in a successively increasing manner when abdominal pain is absent and pancreatic enzymes are decreasing. We aimed to evaluate length of hospital stay (LOHS) and refeeding tolerance for early refeeding and/or immediately full caloric intake in patients recovering from AP.

Methods: In this randomized, open-label trial, patients with AP were randomized into four different refeeding protocols. Group 1 and 2 received a stepwise increasing diet during three days while 3 and 4 received an immediately full caloric, low fat diet. Group 2 and 4 started refeeding early (once bowel sounds returned) and 1 and 3 started at standard time (bowel sounds present, no abdominal pain, no fever, leucocytes and pancreatic enzymes decreasing). Main outcomes measurements were LOHS and tolerance (ability to ingest >50% of meals without severe pain, nausea or AP relapse).

Results: Eighty patients were evaluated and 72 randomized (median age 60 years, range 24–85, 33 male). LOHS was significantly reduced after early refeeding (median 5 versus 7 days (p = 0.001)) but not in patients receiving immediately full caloric diet, compared to standard management (6 versus 6 days (p = 0.12)). There was no difference in refeeding tolerance comparing immediately full caloric diet versus stepwise increasing diet (31/35 (89%) versus 33/37 (89%) patients tolerating the treatment, p = 1.00) or early versus standard time for refeeding (33/37 (89%) versus 31/35 (89%), (p = 1.00)).

Conclusions: Refeeding after AP when bowel sounds are present with immediately full caloric diet is safe and well tolerated. Early refeeding shortens LOHS.

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1. Introduction

Initial treatment of acute pancreatitis (AP) is mainly supportive and consists of pancreatic rest by nil per mouth regimen together with intravenous fluid resuscitation and analgesia [1,2]. Oral nutrition is avoided in order to reduce pain, vomiting and abdominal distension. An additional motive for the pancreatic rest concept is to limit disease progression by avoiding stimulation of pancreatic secretion. This is based on the hypothesis that oral intake in the early phase of AP will stimulate synthesis and secretion of pancreatic enzymes, increase intrapancreatic enzyme activation and thus increase pancreatic tissue damage. Oral refeeding after AP is usually started when patients are free from pain, bowel sounds have returned and serum levels of inflammatory markers and pancreatic enzymes are decreasing [1,3]. Daily caloric and fat intake is usually increased slowly and progressively over several days in order to limit the risk of pain and AP relapse.

However, there is accumulating evidence questioning the rational for pancreatic rest as a mainstay in the management of AP. Human studies have demonstrated that inter digestive exocrine pancreatic secretion is maintained within normal ranges over the first days of disease [4]. Enteral feeding through nasojejunal or even nasogastric tubes has been demonstrated to be safe and reduce the incidence of complications in severe AP compared to parenteral feeding, despite some degree of stimulation of exocrine pancreatic secretion [5,6]. Furthermore, therapies aiming to inhibit exocrine
pancreatic secretion in patients with AP have failed to prove any beneficial effect [7]. The traditional refeeding concept in mild AP has also been challenged in some recent randomized clinical trials (RCT) investigating earlier start of refeeding and alternative and more aggressive refeeding protocols. These studies have consistently demonstrated that early refeeding with low caloric solid diets is well tolerated in cases with mild AP [8–14]. The effect on length of hospital stay (LOHS) has been inconsistent, some studies have demonstrated a reduction [8–10,12,13] while others have not observed any effect [11,14].

The aim of the present study was to simultaneously evaluate a protocol for early refeeding versus standard time and a protocol for refeeding with a full caloric low fat diet versus standard stepwise increasing caloric diet. Main outcome measurement was LOHS. The expected side effect of early and immediately full caloric refeeding is precipitation of gastrointestinal symptoms. An additional aim was therefore to carefully monitor refeeding tolerance and gastrointestinal symptoms after refeeding.

2. Material and methods

2.1. Trial design

This was a randomized, parallel, factorial four-way open-label trial undertaken at the Department of Gastroenterology, University Hospital of Santiago de Compostela, Spain in a period of two years.

2.2. Patients

Patients with AP were eligible for the study. The diagnosis of AP was based on the presence of acute upper abdominal pain and serum amylase or lipase levels higher than three times the upper limit of normal. Exclusion criteria were: inability or unwillingness to understand the study and the informed consent; decreased ability of oral intake for reasons other than those related to AP (e.g. active malignant disease, neurological disease); factors affecting normal pancreatic exocrine function (chronic pancreatitis, prior pancreatic surgery); concomitant diseases affecting diet tolerance (e.g.: diabetes mellitus, celiac disease), pregnancy and lactancy. In addition, initially randomized patients were excluded if they met any of the predefined drop-out criteria; duration of 30 days or more between the onset of symptoms and time when refeeding was possible to start or a need for surgical interventions related to AP complications. Severe acute pancreatitis was defined according to the Atlanta classification [15].

The study was approved by the Ethics Committee of Galicia, Spain, and conducted in accordance with the Declaration of Helsinki and its amendments, and Good Clinical Practice guidelines.

2.3. Treatment assignment and study protocol

Patients meeting inclusion criteria without exclusion criteria were assigned to one of four refeeding protocols; I stepwise increase in caloric intake at standard time, II stepwise increasing caloric intake started early, III immediately full caloric intake started at standard time and IV immediately full caloric intake started early (Table 1). Randomization was done in blocks of four and the randomization sequence was listed in a protocol that was open to assignment according to the randomization sequence list of treatment arms and patients were assigned to one of four treatment groups upon admittance to hospital in a 1:1:1:1 ratio. The stepwise introduction consisted of an increasing caloric intake from 1207, to 1470, to 1767 kcal over three days, whereas the immediate full caloric intake protocol started with the 1767 kcal diet. Early refeeding was initiated as soon as bowel sounds were present. Standard refeeding was initiated when bowel sounds were present, there was no abdominal pain, no fever, decreasing lipase levels and blood leukocyte levels decreasing and below 15000/mm³. Randomization was performed using a predefined list of treatment arms and patients were assigned to a treatment on the basis of the entry number in the study. A minimum period of fasting of 24 h in all groups was required. Pain was treated with iv metamizol every eight hours and iv pethidine on demand for the first 24 h followed by single therapy with iv metamizol on demand started on the second day of admission. Patients were regarded as free of pain if there had been no requirements for analgesics during 24 h.

Refeeding diets consisted of normal solid foods. The nutritional composition of diets used is shown in Table 2. Before refeeding was initiated, oral intake tolerance was tested by letting the patient drink one glass of water. Refeeding was started if this could be ingested without precipitation of abdominal pain, nausea or vomiting to an extent that prevented further oral intake. In those cases, refeeding was postponed and the test was repeated at the time for the next meal.

Criteria for hospital discharge was a fully tolerated full caloric meal (diet III, (Table 2)) followed by an observation period of at least 24 h. In our hospital, cases planned for cholecystectomy are transferred to the Department of Surgery on the day when they otherwise would be fit for discharge. The date for transfer was used as date for discharge in the calculation of LOHS in those cases.

2.4. Baseline data collection

Age, sex, etiology of AP, physiological and biochemical measurements were registered.

2.5. End-points

The primary aim of the study was LOHS, defined as stated above. Gastrointestinal symptoms were registered using a questionnaire.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Start of refeeding</th>
<th>Refeeding schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Standard</td>
<td>Stepwise increase from 1207, to 1470, to 1767 kcal during three days</td>
</tr>
<tr>
<td>II</td>
<td>Early</td>
<td>Stepwise increase from 1207, to 1470, to 1767 kcal during three days</td>
</tr>
<tr>
<td>III</td>
<td>Standard</td>
<td>1767 kcal from start</td>
</tr>
<tr>
<td>IV</td>
<td>Early</td>
<td>1767 kcal from start</td>
</tr>
</tbody>
</table>

a As soon as all of the following criteria are fulfilled: bowel sounds are present, no abdominal pain, no fever, decreasing pancreas specific amylase and blood leukocyte levels decreasing and below 15000/mm³.

b As soon as bowel sounds are present.

Table 2

<table>
<thead>
<tr>
<th>Diet per day</th>
<th>Nutrient</th>
<th>Weight (g)</th>
<th>Energy (kcal)</th>
<th>Percent of total energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Carbohydrates</td>
<td>527</td>
<td>1028</td>
<td>85.2%</td>
</tr>
<tr>
<td></td>
<td>Proteins</td>
<td>20</td>
<td>80</td>
<td>6.6%</td>
</tr>
<tr>
<td></td>
<td>Lipids</td>
<td>11</td>
<td>99</td>
<td>8.2%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>1207</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>Carbohydrates</td>
<td>284</td>
<td>1136</td>
<td>77.3%</td>
</tr>
<tr>
<td></td>
<td>Proteins</td>
<td>43</td>
<td>172</td>
<td>11.7%</td>
</tr>
<tr>
<td></td>
<td>Lipids</td>
<td>18</td>
<td>162</td>
<td>11.0%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>1470</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>Carbohydrates</td>
<td>328</td>
<td>1312</td>
<td>74.3%</td>
</tr>
<tr>
<td></td>
<td>Proteins</td>
<td>71</td>
<td>284</td>
<td>16.1%</td>
</tr>
<tr>
<td></td>
<td>Lipids</td>
<td>19</td>
<td>171</td>
<td>9.7%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>1767</td>
<td></td>
</tr>
</tbody>
</table>

Days refer to stepwise increasing protocol. Patients following the immediately full caloric intake protocol started immediately with the “Day 3” diet.
to ingest less than 50%, more than 50% or 100% of served meals. Any of the following events within 24 h after refeeding:

1. Severe abdominal pain requiring the use of analgesics.
2. Nausea and vomiting that could not be alleviated by metoclopramide.
3. A relapse of AP, defined as a relapse of abdominal pain in combination with an increase in serum pancreatic enzyme levels.
4. Inability to ingest at least 50% of the meals.

All gastrointestinal symptoms after refeeding were prospectively registered. The study protocol did not include any scheduled imaging procedures. Computer tomography was performed on clinical indication if a clinical deterioration was observed during the first 2–3 days despite adequate fluid resuscitation.

2.6. Sample size calculation and statistical analysis of data

Previous studies have demonstrated that a reduction of 2 days in LOHS may be achieved using different rapid refeeding protocols [10,13]. The primary aim of the parallel factorial design was to compare two different treatment strategies in parallel (early refeeding versus standard time for refeeding and stepwise increasing caloric intake versus immediately full caloric intake). Hence, the sample size calculation was based on a comparison of two groups. The number of patients required in order to demonstrate a difference in LOHS of 2 days with 80% power and a significance level of 5% was 36 per aggregated treatment group (72 in total). To account for 10% drop-outs, a total of 80 patients should be allocated refeeding diet, with no differences related to tolerance (Fig. 3).

Data are presented as median values with range. In a first step, the four treatment groups were compared using chi-square and Kruskal–Wallis test. In a second step, the effect of stepwise increasing versus immediately full caloric intake was analyzed comparing groups I and II with groups III and IV, and the effect of standard versus early refeeding was analyzed comparing groups I and III with groups II and IV. Fisher’s exact test and Mann–Whitney U-test were used to calculate p-values. A p-value of <0.05 was considered as statistically significant. All statistical calculations were performed using the software SPSS 19 (Chicago, Illinois, US).

3. Results

Fig. 1 presents a flow chart of patients considered for the study. A total of 80 patients (39 male, 41 female) were initially randomized. Out of these, 8 were excluded because of protocol violations related to missing inclusion criteria or presence of exclusion criteria (one case of alcohol withdrawal syndrome that did not permit refeeding, two cases of malignant active disease, two cases that did not meet diagnostic criteria for AP and three cases with a final diagnosis of chronic pancreatitis). The remaining 72 patients (33 male, 39 female) with AP were finally included in the per-protocol analysis. Sixty-seven cases were mild and five cases were moderate to severe (4 cases with extensive necrosis and one with renal and respiratory insufficiency). Nine patients fulfilled criteria for systemic inflammatory response syndrome (SIRS) at admission. Baseline characteristics are described in Table 3.

3.1. Length of hospital stay

LOHS was significantly shorter in subjects receiving early refeeding compared to those who were refed at standard time (median 5 vs. 7 days, p = 0.001) (Table 5, Figs. 2 and 3). There was no statistically significant difference in LOHS comparing the stepwise increasing protocol to the initial full caloric intake approach (6 vs. 6 days, p = 0.12) (Table 5, Fig. 3). However, immediately full caloric intake was associated with a statistically significantly shorter LOHS in the subgroup of patients that received early refeeding (p = 0.002) (Fig. 4). A statistically significantly shorter LOHS was observed in the group receiving early refeeding with the immediately full caloric protocol when compared individually to all other treatment groups (Fig. 4).

3.2. Refeeding tolerance

Sixty-four out of 72 patients (89%, 95% CI 80–94%) tolerated the allocated refeeding diet, with no differences related to tolerance between the four groups (Table 4). Thirty-one out of 35 (89%, 95%CI 74–95%) patients receiving immediately full caloric diet (groups III and IV) tolerated refeeding compared to 33/37 (89%, 95%CI 75–96%) out of the patients that were fed according to the stepwise increasing caloric protocol (p = 1.00 for difference between treatments). Refeeding was tolerated by 33/37 (89%, 95%CI 75–96%) patients that were refed early compared to 31/35 (89%, 95%CI 74–95%) patients that were refed at standard time (p = 1.00 for difference between treatments).

Among the 8 patients who did not tolerate oral refeeding, one had severe and seven mild AP. Reasons for intolerance are listed in Tables 4 and 5. There were two AP relapse after refeeding, one in...
group IV with a mild alcohol related AP that resolved after five days without complications, and one in group III that relapsed 72 h after refeeding with a combination of signs of cholecystitis and AP.

3.3. Gastrointestinal symptoms after refeeding

Gastrointestinal symptoms after refeeding are reported in Table 4. Overall, 42/72 (58.3%) percent of the patients reported some form of gastrointestinal discomfort. However, there were only 6/72 (8.3%) cases that interrupted refeeding because of gastrointestinal complaints including abdominal pain or inability to finish 50% of the meals. The most frequent gastrointestinal symptoms were meteorism and flatulence (33/72 – 45.8% in total) and postprandial fullness (32/72 – 44.4% in total), occurring in most cases during the first two days after initiation of refeeding. Abdominal pain was registered in 21 cases (29.2%) but led to interruption of refeeding in only 4 (5.6%) cases (including two cases with a relapse of AP).

4. Discussion

Optimal timing and schedule for refeeding in AP was investigated in this prospective, randomized, four way clinical trial. We found that early refeeding decreased LOHS by two days compared to standard refeeding with stepwise increasing caloric intake. Furthermore, early refeeding using a low fat, 1800 kcal diet from the first day as soon as bowel sounds are present was demonstrated to be well tolerated and safe. Gastrointestinal complaints of moderate degree were registered in all treatment schedules with no significant difference between the different treatments strategies. Traditionally, refeeding in AP has been initiated when pancreatic enzymes are decreasing, intestinal peristalsis is present and patients are free from abdominal pain and fever. Oral intake has usually been started with clear liquids followed by solid low fat meals with increasing caloric content over a period of 3–6 days in order to minimize pancreatic stimulation and the risk for abdominal pain and AP relapse [3]. A concern that refeeding will lead to cholecystokinin release, stimulation of exocrine pancreatic secretion and aggravation of pancreatitis has been the theoretical basis the traditional “nil by mouth” management in the early phase of AP. However, this concept has been challenged in a number of recently published studies investigating whether the optimal time for...
refeeding [10,14] or the optimal schedule [9–13] for reintroduction of oral intake. In the present study, we aimed to address both these issues. We did not find any significant difference in tolerance or gastrointestinal symptoms comparing initiation of refeeding early, as soon as bowel sounds were present, or at standard time, when bowel sounds were present, there was no abdominal pain, no fever, decreasing lipase levels and blood leukocyte levels decreasing and below 15000/mm³. However, we observed a significant reduction of LOHS by two days in the early refeeding group. Similar findings has recently been reported from a Chinese randomized clinical trial where refeeding started once patients felt hungry resulted in shorter LOHS compared to refeeding started at routine time, without any significant difference in adverse gastrointestinal events [8]. A German multicentre trial was not able to demonstrate any difference in LOHS when comparing initiation of refeeding in mild AP at the time when patient self preferred given that there was no need for opioid analgesics or when serum lipase was below two times the upper limit of normal [14]. Eckerwall et al. compared two protocols of oral refeeding in mild AP: immediate oral feeding ad libitum and traditional management by initial fasting followed by stepwise reintroduction of oral intake [10]. LOHS was significantly shorter in the early refeeding group (4 vs. 6 days, p < 0.05). However, that study does not allow differentiation of the individual importance of early reintroduction of refeeding and rapid step-up protocol. All studies together clearly demonstrate that normalization of pancreatic enzyme levels is not a prerequisite to restart feeding. Furthermore, early refeeding may shorten LOHS but this was not consistently observed in all studies. The different definitions used for early and standard time for refeeding may explain this discrepancy to some extent.

The next concept that was challenged in the present study was the habit to introduce oral intake in a stepwise manner in subjects with AP. Immediately full caloric diet compared to stepwise increasing caloric intake was not associated with a shorter LOHS in the overall analysis, but in subanalysis of patients given early refeeding. There was no statistically significant difference in tolerance or gastrointestinal symptoms. Different protocols for refeeding in subjects with mild AP have been investigated in five previous RCTs [9–13]. Jacobson et al. compared a clear liquid diet (588 kcal and 2 g of fat per day) to a low–caloric, low-fat diet (1200 kcal and 35 g of fat per day) in patients with mild AP, with no difference in tolerance or LOHS [11]. Moraes et al. performed a study with three treatment arms comparing a hypocaloric clear liquid diet, an intermediate hypocaloric soft diet (both around 250 kcal and 2 and 4 g of fat respectively) and a full solid diet (around 1200 kcal and 30 g fat per day) in patients with mild AP. No differences in pain relapse rates or LOHS between the 3 treatment arms were found [12]. Sathiaraj et al. compared refeeding with a clear liquid diet (458 kcal, 11 g of fat) to a solid diet (1040 kcal and 20 g fat per day) in patients with mild AP. LOHS was significantly reduced in the soft diet group. Finally, Raukmar et al. investigated clear liquid diet compared to soft diet [9]. Total and post-refeeding LOHS was lower in the soft diet group. None of the previously published randomized clinical trials observed any increased risk of refeeding intolerance or other adverse events related to the more active refeeding protocols [9,10,12,13]. In the present study, the refeeding concept of the above-mentioned trials is taken one step further. As reference method, we use a stepwise increasing diet that starts on a caloric content (1207 kcal, 11 g of fat), that is about equal to what has been proven to be feasible in the previous RCTs, and compare this to a
considerably higher caloric intake at day 1 (1800 kcal and 19 g of fat per day).

In subanalysis, we observed that the beneficial effect of immediately full caloric diet was only present when refeeding was started early. Poor statistical power and decreasing tolerance to immediately full caloric diet was only present when refeeding was started early. Postprandial fullness of mild degree that only lead to refeeding sounds necessary.

The absolute number of patients not able to pursue the allocated treatment protocol in our trial was low, 8/72 patients (11%) including 2 cases of relapsing AP in the immediately full caloric intake diet groups. This percentage of AP relapses is in the same range or even lower than what has been observed previously after refeeding in AP in a French multicentre study using a stepwise reintroduction of oral intake (5 out of 116 cases with AP experienced an AP relapse) [17]. As opposed to all previously published RCTs on refeeding in AP, we did not exclude cases with severe AP. There were five severe cases in the study and one out of these were among the 9 cases that did not tolerate reintroduction of oral intake. Assessment of optimal refeeding in severe AP was beyond the scope of this study and no conclusion can be drawn from our findings considering the very small proportion of severe cases.

A total of 58.3% of all patients experienced gastrointestinal symptoms after refeeding. These were mainly meteorism and postprandial fullness of mild degree that only lead to refeeding cessation in three cases. Abdominal pain was registered in 21/72 (29%) patients, but severe enough to interrupt refeeding in only 4/72 (5.6%) cases (2 out of whom had signs of relapse of AP). Recurrent abdominal pain after refeeding in AP has been reported to be 21% and 24% in two previous observational studies [17,18]. However, these results are not directly comparable to ours since refeeding was started despite residual abdominal pain in some patients in the present study.

The present study has several strengths that merit to be pointed out. Patients were included regardless of severity making the findings more easily applicable to clinical practice. Time for refeeding and the refeeding protocol were exactly defined and both parameters were evaluated simultaneously making it possible to differentiate the individual effect of the different interventions. We also used predefined criteria for patient discharge in order to minimize bias related to the physician’s subjective opinion. Gastrointestinal symptoms after refeeding were registered prospectively in a standardized manner.

There are also limitations to the study. We were not able to blind patients or physicians to the treatment. Ideally, randomization should have been performed by sealed envelopes. This was not done in the present study, instead a list that was not concealed to the investigator was used for allocation of patients to different treatment arms. Theoretically, this could introduce a bias in the inclusion of patients into the study. However, the inclusion rate in the current study was high and patients not entered into the study were excluded on the basis of predefined exclusion criteria. It is also not excluded that the lack of blinding has influenced the assessment of symptoms after refeeding. We tried to limit this bias by using a questionnaire and applying strict criteria for outcomes, predefined in the study protocol. Another shortcoming is that although patients with severe AP were not excluded, the proportion of severe cases was low and the conclusions of the study cannot be generalized to the most severe cases of AP. However, in this patient category, LOHS is long and refeeding protocols are a secondary problem in this situation. The number of included patients was moderate in comparison to previous RCTs but predefined and based on a power calculation.

In conclusion, initiation of refeeding in AP once abdominal sounds are present regardless of lipase/amylase levels, leukocyte counts or the presence of abdominal pain, is safe, well tolerated and reduces LOHS by two days compared to standard management. A low fat full caloric oral diet (1800 kcal, 19 g of fat) can be used immediately and a stepwise increase of caloric intake is not necessary.

### Funding

None.

### Conflict of interest

None.
References