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Influence of Early Refeeding on Triglyceride in Patients with Mild Acute Pancreatitis

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The present study aims to explore the influence of early oral refeeding on triglyceride (TG) in patients with mild acute pancreatitis. Eligible patients were randomly divided into the early refeeding group (ER, n = 80) and late refeeding group (LR, n = 77). Both groups received conservative treatment. Patients started refeeding just when they felt hungry in ER group. In LR group, patients didn't restart eating until their serum amylase and lipase decreased to 2 times the upper limits of reference values, the abdominal distension and pain was disappeared with normal bowel sounds. There were 31 patients in ER group and 26 in LR group who's TG were higher than 2.24mmol/L before refeeding. At the time of pre-discharge after refeeding, the number of patients whose TG level decreased were 24 in ER group and 13 in LR group ($p = 0.0307$). (2)There were 24 patients in ER group and 12 in LR group who's TG were higher than 4.48 mmol/L before refeeding. At the time of pre-discharging, the number of patients whose TG were less than 4.48mmol/L was 20 in ER group and 5 in LR group ($p = 0.0015$).(3)The mean refeeding time was 4.63 days in the ER group and 6.83 days in the LR group, respectively ($p < 0.05$). It was concluded that early oral refeeding is beneficial for lipid control in mild acute pancreatitis with hypertriglyceridemia.

Key Words: Mild acute pancreatitis, Early oral refeeding, Triglycerides.

Acute pancreatitis (AP) is a common digestive system disease with pancreatic edema, hemorrhage or necrosis and systematic inflammatory response[1]. The common causes are gallstone and hyperlipemia, especially the hypertriglyceridemia. AP can lead to the injury of other organs, metabolic disorders, including lipidosis. The lipid peroxide can result in systematic inflammatory response and organ injury. So it is an important cause and effect for the disease, which should have drawn much attention during the management.

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Typically, acute pancreatitis needs fasting for some time to inhibit the pancreatic exocrine with total parenteral nutrition(TPN). TPN should not be routinely administered in mild acute pancreatitis or nil by mouth status <7 days, due to high costs and an increased risk of infection[2]. Oral refeeding may be a better choice for the patients with mild acute pancreatitis as soon as possible[3]. Early enteral nutrition seems to play a pivotal role for small and large bowel mucosal integrity, and could prevent the sterile pancreatic necroses from bacterial infection[4]. Several meta-analyses and reviews showed that early enteral nutrition has widely replaced the concept of "pancreatic rest" with long-term enteral starving in patients with severe acute pancreatitis[5-7]. So early oral refeeding may be an important part for the management of AP. Gunilla *et al.*, found that immediate oral feeding

is feasible and safe for mild AP and may accelerate the recovery without adverse gastrointestinal events[8]. Compared with a normal start in patients with predicted severe AP, PYTHON, a multicenter randomized controlled trial, has been designed to show a reduction in the composite primary endpoint of mortality or infections following a very early initiation of enteral nutrition[9]. All these data demonstrated that early oral refeeding is widely accepted for AP.

As we know, hyperlipidemia is closely related with the pathogenesis of AP[10-13]. However, the effect of early oral refeeding on lipids in AP has not been elucidated. The study aims to explore the influence of early oral refeeding on triglyceride in mild acute pancreatitis with hypertriglyceridemia.

MATERIALS AND METHODS

In inclusion and exclusion criteria

The study protocol was defined in accordance with the declaration of Helsinki and was approved by the Hospital Ethics Committees of our institution. After obtaining the informed consent, all adult with AP admitted to the department of integrative medicine in West China Hospital of Sichuan University between January 2009 and December 2009 were enrolled in this study. The diagnosis and severity classification of AP were established according to the consensus of Atlanta. The inclusion criteria were:(1) the onset of acute upper abdominal pain less than 72 hours until hospital admission. (2) presence of upper abdominal pain lasting at least 24 hours associated with elevated serum levels of amylase and/or lipase above 3 times the upper limit of normal and/or an ultrasonic and computerized tomography (CT) scan demonstrating unequivocal evidence of AP and (3) mild AP defined by absence or <30% of pancreatic necrosis if an abdominal CT scan was performed with intravenous contrast bolus and absence of organ dysfunction (shock, respiratory or renal insufficiency, or gastrointestinal bleeding) during hospitalization. The exclusion criteria included: (1) a CT scan with Balzathar CT severity index more than 3 scores, (2) evidences of organ failure lasting 24 hour at any time after hospitalization, (3) AP related complications requiring surgical intervention, (4) received any nutritional support before randomization, (5) AP related complications that were likely to prolong hospitalization, (6) received parenteral analgesic for abdominal pain within 12 hours before randomization, (7) a pancreatic neoplasm or ERCP as etiology of their pancreatitis, (8) patients who had received the surgery affecting oral eating, (9) pregnant or breast feeding women.

The management and oral refeeding protocols

Patients were randomized to early refeeding (ER) group and late refeeding (LR) group. Both groups received conservative treatment, including rehydration, prophylactic antibiotics and a stable internal environment[14]. Patients restarted eating when they feel hungry without the complete remission of abdominal pain and distension in the ER group. For the LR group, patients didn't initiate oral refeeding until their serum amylase and lipase decreased to 2 times of the upper limit of reference value, bowel sounds was normal, the abdominal distension and abdominal pain disappeared.

The hospital discharge was made as successful progression from a liquid meal to a light lipid solid diet with tolerance during an observation period of at least 24 hours. Patients were evaluated on a daily basis until discharge by the attending physician with specific regards to the presence of recurrence of abdominal pain and diet tolerance. The levels of TG, lipase, amylase, albumin, C-reactive protein, blood glucose, and leukocyte counts were examined on admission, then monitored before refeeding and pre-discharge after refeeding. The initiation time of refeeding and tolerance to the oral refeeding also were observed and recorded. After hospital discharge all patients were scheduled an appointment every 5-7 days within 2 months. Pain recurrence during refeeding was defined as the onset of acute abdominal pain demanding parenteral narcotics with or without the need for interruption of oral feeding at any time during hospital stay or the development of abdominal pain requiring hospital readmission up to the seventh day after discharge. After randomization, patients were withdrawn from the trial for noncompliance to the study protocol if they had not accepted the early refeeding or if they did not visited the outpatient department at 7-days intervals after discharge.

The inclusion index of patients' TG level

All patients whose TG level before oral

refeeding was higher than 2.24mmol/L or 4.48mmol/L were screened. TG related parameters of these patients before refeeding and at the time of pre-discharge were compared. The primary outcomes were the changes of triglyceride before oral refeeding and pre-discharge after oral refeeding. The secondary outcomes were the time of oral refeeding after abdominal pain onset.

Statistical Analysis

The outcomes were analyzed with Package for Encyclopaedia Medical Statistics (PEMS) 3.1 for windows medical statistics software. Quantitative data were expressed as median and its variations as mean ± SD when they were normally distributed. Comparisons between the two groups were performed with X^2 test for qualitative data and Student t test or analysis of variance for quantitative data. The level of statistical significance was set at $P<0.05$.

RESULTS

Patient and Disease Characteristics at Baseline

A total of 329 adult patients with AP were screened in the two groups, and 172 patients were excluded as 98 presented evidence of severe AP, while other 74 were excluded for several reasons: time of abdominal pain >3 days before admission (n=56), pregnancy (n=5), and pancreatic neoplasm or ERCP as etiology (n=13). A total of 157 eligible patients were included in the study. There were no significant differences in baseline between the two groups (Table 1).

Table 1. Basic Characteristics of patients

	ER group (n=80)	LR group (n=77)	P Values
Age (years)	49(16—72)	48(11—76)	
Male/female	57/23	50/27	0.3959
Time till admission (day)	1.03 ±0.71	1.12 ± 0.79	0.4536
Etiology			
Biliary	41	38	0.8119
Alcoholic	22	19	0.6871
Miscellaneous	17	20	0.4857
Length of hospitalization(day)	4.63 ±1.59	6.83 ±2.31	0.0000

Serum Triglyceride changes and LOH

The mean days of oral refeeding after abdominal pain onset was 4.63 days in the early refeeding group and 6.83 days in the late refeeding group($p=0.00$). As shown in table 2, the population of patients with abnormal triglyceride was different between the two groups before oral refeeding. TG levels of 9 patients in ER group and 19 patients in LR group rose to some extent before discharge ($p<0.05$). There were 24 patients in ER group and

Table 2. Changes of TG before refeeding and pre-discharge (n)

	ER group (80)	LR group (77)	P values
TG raised after refeeding#	9	19	0.0280
>4.48mmol/l before refeeding	24	12	
<4.48mmol/l before discharge	20	5	0.0015
>2.24mmol/l before refeeding	31	24	
<2.24mmol/l before discharge	4	2	0.4325
Reduction before discharge*	24	13	0.0307

#: TG raised means TG level raised to some extent in all patients of the two groups.
*: Reduction means TG level decreased to some extent but not less than 2.24 mmol/L in patients whose TG were higher than 2.24mmol/L before refeeding.

12 patients in LR group whose TG levels were more than 4.48mmol/L before refeeding. Among them, there were more patients in the ER group than that in LR group who had a significantly lower TG levels before discharge (p=0.0015). In the patients with TG more than 2.24mmol/L before refeeding, there was no statistically significance for the patients whose TG levels were less than 2.24 mmol/L before discharge after refeeding. However, there were much more patients in ER group than that in LR group whose TG decreased to some extent after refeeding, even not less than 2.24mmol/L (p=0.0307).

DISCUSSION

In this study, the results showed that the TG levels in ER group decreased in much more patients than that in LR group. This demonstrated that early oral refeeding seems beneficial for lowering the serum TG in patients with mild AP. Accordingly, the length of hospitalization in ER group was much shorter than that in LR group.

Here the optimal refeeding time was made as patients' feeling of hungry in ER group, without the normalization of laboratory tests or the remission of clinical symptoms and signs. The patients' gastrointestinal function restored when they feel hungry, which demonstrated that they can tolerate the stimulation of food. As shown in this study, hungry may be the indication for oral refeeding, leading to a shorter LOH. Similar to the study that oral refeeding with a soft diet in patients with mild AP can be considered safe and can result in shorter length of hospitalization[13]. So early refeeding may be a good approach for the treatment of mild AP, and hungry may be an indication for refeeding time.

As well as the shorter LOH, early oral refeeding could lead to a lower TG level in mild AP with hypertriglyceridemia. As shown in table 2, there were 19 patients with higher TG in LR group and 9 in ER group before discharge after oral refeeding. The results indicated that early, not the late refeeding could decrease the serum level of TG. For those with TG level higher than 4.48mmol/L, there were much more patients in ER group than that in LR group who's TG level decreased to <4.48mmol/L after oral refeeding. As for those with TG more than 2.24 mmol/L, though there were no statistical significance for the patients with TG less than 2.24mmol/L, 24 out of 31 patients in ER group and 13 out of 24 patients in LR group had a lower TG to some extent ($p<0.05$). The results demonstrated that early oral refeeding may be benefit for TG control in mild AP with hypertriglyceridemia. Some studies have shown that acute pancreatitis itself can lead to hyperlipidemia by the cellulite reduction role of lipoprotein lipase[13]. Oral refeeding and early enteral nutrition are beneficial for the recovery of pancreatitis, and the early restoration of pancreatic exocrine function could promote the metabolism of TG and lead to decline[15].On the other hand, patients had a much shorter time to accept parenteral nutrition support in ER group, which help to decrease the level of serum TG after oral refeeding. As adapted in this study, clear fluid food was administrated to patients first, followed by semi-fluid and liquid diet without lipid. So it could not promote the rise of serum TG level. Meanwhile, patients had a longer time to continue total parenteral nutrition in LR group, which might inhibit the consuming of lipid and lead to higher hypertriglyceridemia.

This single-blind, single center study showed that early refeeding seems to be beneficial to promote TG decline in the mild AP with hypertriglyceridemia. However, the specific mechanisms of early refeeding reduce triglycerides in patients with mild AP is still not elucidated. Early oral refeeding may only be a good factor for TG control in mild AP, rather than determinants. In addition, some studies showed pain relapse during oral refeeding was relatively high in patients with mild AP16, but it had not been observed in this study.

In summary, the study showed that early oral refeeding may be benefit for TG control in mild acute pancreatitis with hypertriglyceridemia. Therefore, patients' feeling of hungry could be considered a well-accepted option for oral refeeding in mild AP with hypertriglyceridemia. But our findings may not be suitable for patients with severe AP as only individuals with mile AP were included in this study.

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REFERENCES

1. Bradley EL. A clinically based classification system for acute pancreatitis: summary of the Atlanta symposium. *Arch Surg*. 1993; **128**(5): 586–590.
2. Schulz RJ, Bischoff SC, Koletzko B.Gastroenterology - Guidelines on Parenteral Nutrition, Chapter 15. Working group for developing the guidelines for parenteral nutrition of The German Association for Nutritional Medicine. *Ger Med Sci*. 2009; **7**: 1-6.
3. Teich N,Aghdassi A,Fischer J,Walz B,Caca K,Wallochny T,von Aretin A, von Boyen G,Göpel S,Ockenga J. Optimal Timing of Oral Refeeding in Mild Acute Pancreatitis: Results of an Open Randomized Multicenter Trial. *Pancreas*, 2010; **39**(7): 1088-1092.
4. Ammori BJ. Role of the gut in the course of severe acute pancreatitis. *Pancreas*. 2003; **26**(2):122-129.
5. Koretz RL. Enteral nutrition: a hard look at some soft evidence. *Nutr Clin Pract.* 2009; **24**(3): 316-324.
6. Moraes JM, Felga GE, Chebli LA, Franco MB, Gomes CA, Gaburri PD ,Zanini A,Chebli, J.M.F. A Full Solid Diet as the Initial Meal in Mild Acute Pancreatitis is Safe and Result in a Shorter Length of Hospitalization:Results From a Prospective, Randomized, Controlled,Double-blind Clinical Trial. *J Clin Gastroenterol*, 2010; **44**(7): 517-22.
7. Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. *Dig Surg*, 2006; **23**(5-6): 336–345.
8. Gunilla E. Eckerwall, Bobby B.Tingstedt, Per E, Andersson, R.G. Bergenzaun, Anderson RG. Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery—A randomized clinical study. *Clinical Nutrition*, 2007; **26**(6), 758–763.
9. Bakker OJ, van Santvoort HC, van Brunschot S, Ahmed Ali U, Besselink MG, Boermeester MA *et al*. Dutch Pancreatitis Study Group. Pancreatitis, very early compared with normal start of enteral feeding (PYTHON trial): design and rationale of a randomised controlled multicenter trial. *Trials*, 2011; **10**; 12(1):73.
10. WanYJÿSun JB, Li F,Zhang S.W.. Hyperlipidemia intensifies cerulein-induced acute pancreatitis associated with activation of protein kinase C in rats. *World J Gastroenterol* 2006; **12**(18), 2908-2913.
11. Unal E,Uzun H,Kusaslan R,Dogan M,Genc H,Gunes P,Titiz I. Serum Paraoxonase Activity and Lipid Profile in Experimental Acute Pancreatitis. *Pancreas* 2005; **31**(1): 84–87.
12. Xu ZR. Influence of the correlation of Lipid levels and acute pancreatitis. *J Chin Modern Med* 2007; **4**: 1032-1033.
13. Knobell R, Castilho LN, Passini R, Parentoni L.S ,Faria E.C.D. Hyperlipidemic pancreatitis in a primigravida adolescent. *Dig Dis Sci* 1998; **43**(5): 943- 944.
14. Gong HL, Tang WF, Ren YY, Wan MH, Chen GY, Xia Q, Huang, Xi. Summary of integrative medicine for severe acute pancreatitis: 26-year clinical experiences and a report of 1 561 cases. *Chin J Integr Med.* 2011; **17**(5):381-5.
15. Pezzilli R, Simoni P, Casadei R, Morselli-Labate AM.Exocrine pancreatic function during the early recovery phase of acute pancreatitis. *Hepatobiliary Pancreat Dis Int*, 2009; **8**(3): 316-319.
16. Chebli J,Fonseca M,Gaburri P.D,Desouza A.F.M,Junior E.V,Gaburri A.N. A. K, Felga G.E.G,Depaula E.A,Forn C.G,Dealmeida G.V. Oral refeeding in patients with mild acute pancreatitis: Prevalence and risk factors of relapsing abdominal pain. *Journal of Gastroenterology and Hepatology* 2005; **20**(9): 1385–1389.