Early Enteral Nutrition Prevent Acute Pancreatitis From Deteriorating in Obese Patients

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Goals: The aim of this study was to determine a potential strategy to prevent acute pancreatitis (AP) from deteriorating in obese patients.

Background: Nutritional support plays a critical role in the treatment of AP. Early enteral nutrition (EEN) is considered to be able to protect mucosa of AP patients and alleviate inflammatory reactions. Obesity worsen AP prognosis. However, little is known about the effects of EEN in obese patients.

Study: Prospective randomized control trial. Subjects with moderately severe AP or severe AP were divided into the visceral fat obesity (VFO) group and the non-VFO group by obesity index VFO. The patients received "delayed" enteral nutrition (started enteral nutrition feeding after the first 48 hours after admission to the hospital: group A: patients of non-VFO, n = 108; group B: VFO patients, n = 88) or EEN (in the VFO subgroup, group C: n = 91). Occurrence of complication, clinical outcomes, plasma levels of cytokines, and intestine gut barrier index were measured at different timepoints after admission.

Results: VFO was a risk factor for aggravating of AP. EEN prevented the VFO patients from developing pancreatic necrotic infection, the mechanism of which might be related with inhibiting excessive inflammatory reactions, adjusting the imbalance of inflammatory response, and alleviating ischemia of intestine mucosa.

Conclusions: The potential strategy, EEN, was able to prevent AP from deteriorating in obese patients.

Key Words: early enteral nutrition, acute pancreatitis, obese patients, VFO

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The prevalence and incidence of obesity are increasing rapidly in both developed and developing countries in the Asia-Pacific area.[1] Several larger studies have provided convincing evidence of the adverse effect of obesity on acute pancreatitis (AP).[2–5] Although increasing evidence has confirmed the aggravating effect of obesity on the course and prognosis of AP, no effective strategy is available to prevent AP from deteriorating in obese patients.

Nutritional support plays a critical role in the treatment of moderately severe acute pancreatitis (MSAP)/severe acute pancreatitis (SAP). Several randomized controlled studies and meta-analysis have shown the benefits of enteral nutrition (EN) over parenteral nutrition (PN) in SAP, primarily in lower risk of pancreatic infections and mortality.[6–12] There was controversy over the timing of the EN. Early enteral nutrition (EEN) has been considered to be able to protect mucosa of AP patients and alleviate inflammatory reactions in previous study. In contrast, a recent study published in the *New England Journal of Medicine* (NEJM) did not show the superiority of early nasoenteric tube feeding, as compared with an oral diet after 72 hours, in reducing the rate of death in patients with AP at high risk for complications.[12] However, in these studies, little information has focused on effects of nutritional support management on obese patients, one kind of common and special patients with AP. A subset of obese patients may be the key to controversy. In our study, we used visceral fat obesity (VFO) to define obesity and we divided patients with MSAP/SAP into VFO and non-VFO groups to explore effects of VFO on AP. And we conducted delayed EN (DEN) or EEN in the VFO subgroup to confirm the impact of feeding timing on prognosis of AP in the VFO subgroup. Possible mechanisms were studied in an attempt to find out effective strategy available to prevent AP from deteriorating in VFO patients.

METHODS

Patients

The study was conducted in the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, from September 15, 2014 to October 31, 2016. All studies were conducted in compliance with International Conference on Harmonisation Good Clinical Practice guidelines and the World Medical Association Declaration of Helsinki and its amendments. Local institutional review boards or medical ethics committees approved all protocols. The registration number was 2015-05. Written informed consent was obtained from all the patients or their responsible relatives before enrollment.

Diagnosis of AP

The diagnosis of AP involves a combination of symptoms, physical examination, and focused laboratory values and requires 2 of the following 3 features: (1) upper abdominal pain of acute onset often radiating through to the

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back; (2) serum amylase or lipase activity > 3 times normal; and (3) findings on cross-sectional abdominal imaging consistent with AP. We stress that not every patient requires pancreatic imaging to make the diagnosis, provided the clinical picture is that of AP.[13]

MSAP has transient organ failure (organ failure of <2 d), local complications, and/or exacerbation of coexistent disease. SAP is defined by the presence of persistent organ failure (organ failure that persists for ≥2 d). Local complications are defined by objective criteria based primarily on contrast-enhanced computed tomography (CT); these local complications are classified as acute peripancreatic fluid collections, peripancreatic pseudocyst, acute (pancreatic/peripancreatic) necrotic collection, and walled-off necrosis.[14]

Groups

Patients with visceral fat area (VFA) ≥ 100 cm^2 by CT[15] were assigned into a VFO group, otherwise assigned into an non-VFO group. Those patients who met the inclusion were then assigned to 1 of the 3 treatment groups: group A: patients of non-VFO who started EN feeding after the first 48 hours after admission to the hospital (DEN); and group B: VFO patients in whom EN feeding was started 48 hours after admission (DEN). Group C: VFO patients in whom EN feeding was started within 48 hours after admission to hospital ("early" EN, EEN). A nasojejunal tube for enteral feeding was inserted by a medical staff, and the position of the tube was checked on radiographs. In patients in whom the passage of the tube tip beyond the Treitz ligament was not achieved, the tube was endoscopically inserted. And gastrointestinal events were recorded in 3 groups, respectively. EEN for all patients must be finished within 48 hours after admission. DEN for all patients must be finished 48 hours after admission.

EN Implementation Scheme

EN was used as the main energy supply substance with short peptide nourishment, and Enteral Nutritional Suspension (SP, Nutrica Co., Holland) was infused through the nasal jejunum tube or the jejunum ostomy tube. At the beginning, the normal saline was entered into the jejunum through the nasal jejunum tube or the jejunum ostomy tube, 20 to 30 mL/h. If the patients could tolerate well, the Enteral Nutritional Suspension was dripped after 2 to 4 hours, the initial dosage was 25 mL/h, and the dosage of the Enteral Nutritional Suspension was gradually increased after 24 to 48 hours, and increased to about 80 to 90 mL/hours within 7 to 10 days, adjusted according to the total quantity of calorie required. At the beginning of the EEN group, the nonprotein calorie was (12.6 ± 2.3) kcal/kg/d, and gradually increased to (29.1 ± 5.7) kcal/kg/d. In the first few days, due to insufficient calorie and nitrogen, EN needs to be supplemented by intravenous nutrition.

Comparison of Prognostic Scores

Along with enteral feeding, the patients were managed by standard medical treatment in AP: intravenous fluid and electrolytes, analgesia, prophylactic antibiotics, and other supportive therapies for organ failure, as indicated. All the patients were assessed daily by monitoring the scores of APACHE-II[16] for 7 days after treatment. On posttreatment the fifth day, abdominal ultrasonography was performed to screen inflammatory pancreas. Contrast-enhanced abdominal CT scans were performed on the fifth day after treatment when the pancreatitis could not be adequately visualized or there was obvious peripancreatic edema, fluid collection, or vessel complications as detected by ultrasound, and CTSI (CT severity index) was also evaluated in every patient.[16] Intensive care and supportive treatments were conducted in patients whose condition progressed into SAP according to the guideline of SAP.[17] Emergency endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic papillotomy within 24 to 72 hours was performed in patients with persistent jaundice or cholangitis.[18] Patients were discharged when they had no fever, no abdominal pain, and could tolerate oral diet. The clinical course, complications, and investigations were documented in all patients until discharge from the hospitals or death. Follow-up evaluations after discharge were performed during study day 28 to day 30, including clinical manifestations, abdominal ultrasound, or CT scan to detect any local complications such as pseudocyst, abscess, and obstruction of the splendid vein.

Risk Factors for Mortality of Patients With MSAP or SAP

Both univariate and multivariate logistic regression analyses were performed. The factors included in the present investigation were age, sex, etiology, C-reactive protein (CRP) on admission, serum tumor necrosis factor alpha (TNF-α) level on admission, serum interleukin (IL)-8 level on admission, serum IL-10 level on admission, VFA, APACHE-II scores on admission, and method of administration of EN. All these parameters were assessed, and all the laboratory results were studied at the central laboratory of the Second Affiliated Hospital of Wenzhou Medical University. Mortality of patients was recorded to establish the prognosis of patients with MSAP or SAP.

Serum Collection and Measurement

Serum vials for the analysis of intestinal fatty acid binding protein (I-FABP) and citrulline were separated at the timepoints of collection and kept deep frozen at −80°C until measurement.[19,20] We tested the serum level of I-FABP using enzyme-linked immunosorbent assay according to the instruction manual (ADL Co., Mukwonago, WI). The microtiter plate we used had been precoated with an antibody specific to human I-FABP. The samples and I-FABP standards were pipetted into these wells with a biotinylated monoclonal antibody specific for I-FABP and incubated for 60 minutes at 37°C. After washing, the enzyme (streptavidin-peroxydase) was added and allowed to incubate for 30 minutes at 37°C. After washing again, substrates A and B were added and incubated for 15 minutes. And then, the reaction was stopped, and absorbance was read at 450 nm. The intensity of this colored product was directly proportional to the concentration of I-FABP present in the samples. The serum level of citrulline concentration was considered as the parameter of absorption function of gut and was determined by high-performance liquid chromatography (Waters, Milford, MA).[19,20]

We assessed the inflammatory response in AP by measuring serum concentrations of CRP, TNF-α, IL-8, and IL-10. Serum samples collected at different time after admission were assayed for CRP, IL-8, and IL-10 levels, quantified using a fluorescence-based capture sandwich immunoassay.[21] TNF-α was measured with radioimmunoassay kits (iodine ^{125}I-TNF-α; Radio immunity Research Institute, General Hospital of Chinese PLA, Beijing, China).

TABLE 1. Characteristics of Study Patients

Variables	Pair 1		Pair 2		
	Group A (N = 108)	Group B (N = 88)	Group C (N = 91)	Pair 1 (*P*)	Pair 2 (*P*)
Age (y) [$\bar{x}$ (s)]	46 (13)	46 (12)	48 (14)	0.895	0.329
Gender (male/female) (N)	65/43	56/32	57/34	0.659	1.000
VFA (kg/m^2) [$\bar{x}$ (s)]	83.6 (10.6)	127.8 (28.7)	133.9 (18.9)	0.000	0.093
Etiology (N)				0.544	0.515
Biliary	68	52	60		
Alcohol	23	16	17		
Hyperlipidemic	9	16	11		
Idiopathic	5	4	3		
Post-ERCP	3	0	0		
APACHE-II score on admission [$\bar{x}$ (s)]	8.2 (3.5)	9.1 (3.5)	9.3 (3.4)	0.087	0.860
CTSI ≥ 6 [n (%)]	32 (29.6)	43 (48.9)	32 (35.2)	0.006	0.088

Pair 1 (*P*): *P*-value of group A versus group B; pair 2 (*P*): *P*-value of group B versus group C.
CTSI indicates computed tomographic severity index; ERCP, endoscopic retrograde cholangiopancreatography; VFA, visceral fat area.

Statistical Analysis

Data were collected and entered into a database for analysis (SPSS version 11.5 for Windows). Statistical analysis was performed with the Levene test for equality of variances, the independent samples *t* test, and a χ^2 test to examine differences between the groups. To identify the risk factors for mortality of MSAP or SAP, several series of univariate logistic regression analyses using the 10 forementioned indices were performed. Variables which were $P < 0.10$ and considered potentially clinically significant were included in the multivariate analysis, and a multiple logistic regression analysis was performed; $P < 0.05$ was considered significant.

RESULTS

Patients' Characteristics

In total, 179 patients (62.3%) were VFO patients (VFA ≥ 100 cm^2). The mean age is 47 years (ranging from 15 to 90 y). The mean VFA was 127.8 cm^2 in group B, and 133.9 cm^2 in group C, which were significantly > 83.6 cm^2 in group A ($P < 0.05$), respectively. Etiologic classification of MSAP/SAP included biliary in 180 patients (62.7%), post-ERCP procedure in 3 patients (1.0%), idiopathic in 12 patients (4.2%), alcohol-associated in 56 patients (19.5%), and hypertriglyceridemia in 36 patients (12.5%). Moreover, the percentage of patients with CTSI ≥ 6 in group B was significantly higher than that in group A ($P < 0.05$), but there is no significantly difference between group B and group C ($P > 0.05$) (Table 1).

Comparative Analysis of Different Prognostic Scores

The assessment of the severity of AP in the study patients by using APACHE-II score is shown in Table 2. The APACHE-II score on admission in group A, group B, and group C was (8.2 ± 3.5), (9.1 ± 3.5), and (9.3 ± 3.4), respectively, showing no significant difference between 3 groups on admission ($P > 0.05$). In group A, a gradual decrease in APACHE-II scores over the study days was observed, significantly lower than group B on the third and the seventh day ($P < 0.05$). On the seventh day, but not on the third day, significant difference was also observed between group B and group C ($P < 0.05$).

Occurrence of Complication and Clinical Outcomes

Table 3 reports on the main clinical outcomes and complications in 3 groups. Overall, the hospital stay day was (22 ± 12) days in group A, (26 ± 13) days in group B, and (22 ± 13) days in group C, respectively. There was significant difference between group B and group C ($P < 0.05$), but not between group A and group B ($P > 0.05$). Moreover, 126 patients (43.9%) of the all 287 patients underwent surgical treatment or interventional therapy during hospitalization: 43 patients (39.8%) in group A, 48 patients (54.5%) in group B, and 35 patients (38.5%) in group C. Surgical procedures comprised the following: debridement of necrosis with lavage and drainage of infected net necrosis. The percentage of patients admitted to the intensive care unit in group B (28 cases, 31.8%) was significantly higher than that in group A (19

TABLE 2. Assessment of AP in Study Patients by Using APACHE II Score System of 3 Groups

Variables	Pair 1	Pair 2			
	Group A (N = 108)	Group B (N = 88)	Group C (N = 91)	Pair 1 (*P*)	Pair 2 (*P*)
APACHE II					
On admission	8.2 ± 3.5	9.1 ± 3.5	9.3 ± 3.4	0.087	0.860
Day 3	8.0 ± 2.6	9.5 ± 3.5	8.8 ± 3.4	0.001	0.191
Day 7	7.5 ± 3.3	9.2 ± 4.1	7.9 ± 3.1	0.001	0.014

Pair 1 (*P*): *P*-value of group A versus group B; pair 2 (*P*): *P*-value of group B versus group C.

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TABLE 3. Clinical Outcomes of 3 Groups

	Pair 1		Pair 2		
Variables	**Group A (N = 108)**	**Group B (N = 88)**	**Group C (N = 91)**	**Pair 1 (*P*)**	**Pair 2 (*P*)**
MSAP/SAP (n/n)	91/17	63/25	66/25	0.036	1.000
Hospital stay ($\bar{x} \pm s$) (d)	22 ± 12	26 ± 13	22 ± 13	0.016	0.0002
Surgery/interventional therapy (n)	43	48	35	0.045	0.036
ICU (n)	19	28	27	0.028	0.871
Local complications (n)					
Acute peripancreatic fluid collections	64	32	34	0.002	1.000
Acute necrotic collections	44	56	57	0.002	1.000
Pseudocyst	28	24	19	0.872	0.382
Walled-off necrosis	13	33	28	0.000	0.350
Necrotic infection	10	24	13	0.001	0.042
Organ dysfunction (n)					
Acute respiratory failure	13	23	13	0.015	0.062
Acute renal failure	9	10	12	0.480	0.821
Heart failure	11	8	9	1.000	1.000
Shock	9	16	14	0.052	0.691
Mortality (n)	2	5	4	0.246	0.744

Pair 1 (*P*): *P*-value of group A versus group B; pair 2 (*P*): *P*-value of group B versus group C.
ICU indicates intensive care unit; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis.

cases, 17.6%) ($P < 0.05$), but not between group B and group C ($P > 0.05$).

Contrast-enhanced CT scan showed peripancreatic fluid collection in 64 patients (59.2%) in group A and 32 patients (36.4%) in group B ($P < 0.05$). Pancreatic necrotic collections was reported in 44 patients (40.7%) in group A and 56 patients (63.6%) in group B ($P < 0.05$). Pancreatic walled-off necrosis was reported in 13 patients in group A and 33 patients in group B ($P < 0.05$). Pancreatic infected necrosis was reported in 10 patients in group A and 24 patients in group B ($P < 0.05$). There were also no differences regarding pancreatic pseudocyst between group A and group B ($P > 0.05$). So, VFO increased the risk of peripancreatic fluid collection, pancreatic necrotic collections, pancreatic walled-off necrosis, and infected necrosis. The incidence of pancreatic infected necrosis in group C decreased to 14.3% after EEN, significantly lower than that in group B ($P < 0.05$), although still higher than that in group A, suggesting that EEN can decrease the risk of pancreatic infected necrosis in VFO patients with MSAP/SAP. However, there was no significant difference regarding peripancreatic fluid collection, pancreatic pseudocyst, pancreatic necrotic collections, and pancreatic walled-off necrosis between group B and group C ($P > 0.05$).

Overall, pulmonary failure occurred in 13 patients (12.0%) in group A and 23 patients (26.1%) in group B ($P < 0.05$). No significant differences between group A and group B were noted in the percentage of acute renal failure, shock, and cardiovascular failure ($P > 0.05$). When analyzing the incidence of respiratory failure, renal failure, cardiovascular failure, and shock between group B and group C, there was also no significant difference shown ($P > 0.05$). So, EEN did not significantly decrease the risk of pulmonary failure, renal failure, cardiovascular failure, and shock in VFO patients with MSAP/SAP, when compared with VFO patients with DEN ($P < 0.05$).

The mortality was 1.8% (2/108) in group A, 5.7% (5/88) in group B, and 4.3% (4/91) in group C, showing no significant difference between group A and group B, group B and group C, respectively ($P > 0.05$). All 11 patients who died were hospitalized in intensive care unit because of multiple organ failure.

Risk Factors for Mortality of MSAP and SAP

Bringing these 10 variables into the univariate logistic regression analyses, we proved 3 variables to be potentially clinically significant: VFA $\geq 100\,cm^2$, serum CRP level on admission, and APACHE-II score (≥ 16). The 3 risk factors were then included in the multivariate analysis, indicating that VFA (VFA $\geq 100\,cm^2$) and APACHE-II score (≥ 16) were independent risk factors for mortality of patients with MSAP or SAP (Table 4).

Serum Level of Cytokines

Serum levels of CRP, IL-8, TNF-α, and IL-10 in all MSAP/SAP patients are presented in Table 5. The serum levels of CRP (on the first, third, and the seventh day after admission), TNF-α (on the third and the seventh day after

TABLE 4. Risk Factors for Mortality of Patients With MSAP or SAP

							95% CI for Exp (*B*)	
Variables	***B***	**SE**	**Wald**	***df***	**Sig.**	**Exp (*B*)**	**Lower**	**Upper**
VFA ($\geq 100\,cm^2$)	−1.195	0.399	7.565	1	0.004	0.2893	0.119	0.711
APACHE (≥ 10)	−3.198	1.102	12.13	1	0.001	0.031	0.004	0.294

CI indicates confidence interval; *df*, degree of freedom; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; sig., significant; VFA, visceral fat area.

TABLE 5. Plasma Levels of Cytokines of 3 Groups on Admission, Day 3, and Day 7 After Admission

	Pair 1		Pair 2		
Serum Cytokines	**Group A (N = 108)**	**Group B (N = 88)**	**Group C (N = 91)**	**Pair 1 (*P*)**	**Pair 2 (*P*)**
CRP (mg/L)	103.5 ± 25.8	133.7 ± 40.7	142.4 ± 45.9	0.000	0.1819
TNF-α (pg/mL)	1142.0 ± 570.6	1171.0 ± 304.7	1094.7 ± 306.5	0.668	0.097
IL-8 (pg/mL)	106.0 ± 9.6	146.5 ± 10.1	144.5 ± 42.8	0.000	0.673
IL-10 (pg/mL)	175.9 ± 51.0	252.8 ± 54.1	241.1 ± 55.5	0.000	0.151
CRP (day 3) (mg/L)	114.4 ± 23.7	145.8 ± 37.8	122.3 ± 34.8	0.000	0.001
TNF-α (day 3) (pg/mL)	1336.6 ± 93.7	1848.4 ± 112.5	1639.7 ± 197.1	0.000	0.000
IL-8 (day 3) (pg/mL)	126.8 ± 9.8	176.4 ± 17.0	131.8 ± 35.9	0.000	0.000
IL-10 (day 3) (pg/mL)	130.5 ± 29.2	171.7 ± 37.9	174.4 ± 78.1	0.000	0.772
CRP (day 7) (mg/L)	78.4 ± 16.3	118.8 ± 24.5	89.4 ± 22.0	0.000	0.000
TNF-α (day 7) (pg/mL)	971.1 ± 174.9	1386.5 ± 159.7	1049.1 ± 137.7	0.000	0.000
IL-8 (day 7) (pg/mL)	76.2 ± 7.5	98.1 ± 7.6	97.8 ± 15.3	0.000	0.857
IL-10 (day 7) (pg/mL)	64.5 ± 14.2	124.7 ± 27.5	202.8 ± 27.0	0.000	0.000

Pair 1 (*P*): *P*-value of group A versus group B; pair 2 (*P*): *P*-value of group B versus group C.
CRP indicates C-reactive protein; IL, interleukin; TNF, tumor necrosis factor.

admission), IL-8 (on the first, the third, and the seventh day after admission), and IL-10 (on the first, the third, and the seventh day after admission) in group B were significantly higher than those in group A ($P < 0.05$). Compared with group B, the serum levels of CRP (on the third and the seventh day after admission), the serum levels of TNF-α (on the third and the seventh day after admission) and IL-8 (on the third day after admission) in group C decreased significantly after EEN, respectively ($P < 0.05$). Compared with group B, the serum levels of IL-10 (on the seventh day after admission) in group C increased significantly after EEN ($P < 0.05$).

Gastrointestinal Events in 3 Groups

Gastrointestinal events in all MSAP/SAP patients were presented in Table 6, showing there was no significant difference between group A and B, also between group B and group C regarding nausea, vomiting, aspiration, ileus, and diarrhea, respectively ($P < 0.05$).

Serum Level of I-FABP and Citrulline Level

Serum level of I-FABP and citrulline in all MSAP/SAP patients are presented in Table 7. The serum levels of I-FABP (on the third and the seventh day after admission) in group B were significantly higher than those in group A ($P < 0.05$), respectively. The serum levels of citrulline in group B (on the third and the seventh day after admission) were significantly lower than those in group A, respectively ($P < 0.05$). Compared with group B, the serum levels of I-FABP (on the third and seventh day after admission) in group C decreased significantly after EEN, respectively ($P < 0.05$). Compared with group B, the serum levels of citrulline (on the third and seventh day after admission) in group C increased significantly after EEN, respectively ($P < 0.05$).

TABLE 6. Gastrointestinal Event of 3 Groups

	n (%)				
	Pair 1		Pair 2		
Variables	**Group A (N = 108)**	**Group B (N = 88)**	**Group C (N = 91)**	**Pair 1 (*P*)**	**Pair 2 (*P*)**
Nausea	32 (29.9)	32 (36.3)	33 (36.2)	0.474	0.670
Vomiting	23 (21.4)	24 (27.2)	18 (19.7)	0.436	0.338
Aspiration	3 (2.80)	4 (4.5)	0 (0)	0.341	0.199
Ileus	8 (26.7)	12 (13.5)	8 (8.7)	0.231	0.535
Diarrhea	26 (24.2)	28 (31.8)	20 (21.9)	0.348	0.246

Pair 1 (*P*): *P*-value of group A versus group B; pair 2 (*P*): *P*-value of group B versus group C.

DISCUSSION

It is well known that obesity increased the risk of AP.[2–4] Because the prevalence and incidence of obesity are increasing rapidly in both developed and developing countries in the Asia-Pacific area, more and more attention has been attached to AP in obese patient.[1] At present, there are a lot of indicators for definition of obesity, such as body mass index, waist to hip ratio, waist circumference, and other physical indicators.[22–24] However, these indices do not accurately reflect the accumulation of visceral fat and the distribution of fat in the abdominal cavity. For AP patients, the visceral fat content, especially the fat content around the pancreas, and the total inflammatory factors released by it, are the key factors affecting the prognosis of patients with AP. VFA measured by CT can directly reflect intra-abdominal fat accumulation and fat distribution. Therefore, theoretically, VFO (defined by VFA $\geq 100\,cm^2$) may be more suitable for studying obese patients with AP.[15] In our study, we used VFO to define obesity.

In this study we found that VFO increased the risk of developing local complications (acute peripancreatic fluid collection, acute pancreatic necrotic collection, walled-off necrosis, and pancreatic necrotic infection) and rate of acute respiratory failure, which is in accordant with the reports of previous studies.[25,26] To explore the possible mechanism of increasing risk of AP in VFO patients, CRP and proinflammatory cytokines TNF-α, IL-8, and anti-inflammatory cytokine IL-10 were measured in non-VFO patients and VFO patients. On the pancreatic view, TNF-α, IL-8, and IL-10 have a major role on the pathophysiology of AP, as part of the inflammatory network evoked systemically.[27] Previous studies have showed that CRP were significantly higher in overweight patients compared with nonoverweight patients.[3] TNF-α and IL-8 were significantly higher in patients with central fat distribution compared with patients with noncentral fat distribution.[28,29] IL-10 were increased in the AP group in comparison with the control group, and the

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TABLE 7. Intestine Gut Barrier Index of 3 Groups on Admission, Day 3, and Day 7 After Admission

	Pair 1		Pair 2		
Serum Cytokines	**Group A (N = 108)**	**Group B (N = 88)**	**Group C (N = 91)**	**Pair 1 (*P*)**	**Pair 2 (*P*)**
I-FABP (pg/mL)	143.6 ± 38.9	144.1 ± 50.3	156.3 ± 44.9	0.937	0.090
Citrulline (μmol/L)	7.2 ± 3.2	7.1 ± 4.0	7.0 ± 2.9	0.878	0.857
I-FABP (day 3) (pg/mL)	151.4 ± 42.5	196.4 ± 34.3	140.5 ± 27.3	0.000	0.000
Citrulline (day 3) (μmol/L)	6.1 ± 2.3	4.9 ± 1.8	8.5 ± 2.9	0.000	0.000
I-FABP (day 7) (pg/mL)	137.6 ± 49.4	166.2 ± 29.9	115.3 ± 18.8	0.000	0.000
Citrulline (day 7) (μmol/L)	8.0 ± 2.4	6.8 ± 2.4	9.3 ± 3.5	0.001	0.000

Pair 1 (*P*): *P*-value of group A versus group B; pair 2 (*P*): *P*-value of group B versus group C.
I-FABP indicates intestinal fatty acid binding protein.

IL-10 levels was significantly increased in patients with severe AP.[29] It was also found that the serum levels of IL-10 maintains correlating with serum levels of TNF-α and IL-6 as observed in previous study.[30] Our study found that the serum levels of TNF-α (on the third and the seventh day after admission), IL-8 (on the first, the third, and the seventh day after admission), and IL-10 (on the first, the third, and the seventh day after admission) in VFO group were significantly higher than those in non-VFO group. Unlike previous studies which focused on effects of obesity (based on body mass index) on AP, our studies explored effects of VFO on AP, and measured serum levels of IL-6, IL-10, and TNF-α level in VFO patients, but similar results were obtained as before. So our study indicated that VFO aggravated AP by amplifying inflammatory reactions, manifested by increase of CRP, IL-6, IL-10, and TNF-α. Moreover, in our study we also measured the serum level of I-FABP and citrulline in patients. I-FABP acted as a direct indicator for the gut ischemia, and citrulline as an important source of endogenous arginine. I-FABP is a 15 kd protein that is uniquely located at the tips of intestinal mucosal villi.[19] It indicates the gut epithelial cells' injury in the very early phase. Citrulline is an important source of endogenous arginine.[20] Reduced plasma citrulline levels is a quantitative biomarker of significantly reduced enterocyte mass and function in different disease states in human.[20] Previous study in acute pancreatitis has showed that the serum level of I-FABP increased on admission, and it was more pronounced in severe attacks with decreased serum level of citrulline. A reverse correlation between the serum level of I-FABP and the serum level of citrulline was found.[31] But in obese patients with AP, the level of I-FABP and citrulline regarding the possible ischemia of intestine mucosa were still not studied up to now. In our study we found that serum level of I-FABP (on the third and the seventh day after admission) in VFO patients were significantly higher than those in non-VFO patients ($P < 0.05$), respectively. The serum levels of citrulline in VFO patients on the third and the seventh day were significantly lower than those in non-VFO patients, respectively ($P < 0.05$), indicating that ischemia of intestine mucosa may exist in VFO patients with MSAP/SAP. On the basis of our study, we can believe that VFO was a risk factor for aggravating of AP. The mechanism of which might be related with excessive inflammatory reactions, imbalanced inflammatory response, and ischemia of intestine mucosa.

And in our study we also found that EEN within 48 hours after admission greatly reversed the incidence of pancreatic infected necrosis, but not rate of respiratory failure, compared with DEN in VFO patients with MSAP/SAP.

It was well known that prolonged fasting can potentially lead to bacterial translocation across the gut barrier and complications.[32] Bacterial translocation from the gut has been considered a central mechanism underlying the development of the pancreatic infections of necrosis.[33,34] Previous studies have shown that EN has a bigger effect on serum endotoxin and intestinal permeability in patients with SAP when compared with PN. EN can better promote the elimination of serum endotoxin and reduce intestinal permeability.[35] EEN was initiated in early phase of AP, commonly within 3 to 5 days after admission. But among patients with SAP, limited evidence revealed no statistically significant difference in outcomes between early and delayed feeding.[36] But these studies have not performed risk-stratify analysis for AP. VFO acted as a risk factor for aggravating of AP, it is necessary to perform analysis for VFO patients with AP specially. For VFO patients, because of its susceptibility to infection owing to extensive fat tissue and relatively weak resistance, can EEN bring benefits for VFO patients when attacked by MSAP/SAP? Fortunately, our results indeed found the EEN reversed the incidence of pancreatic infected necrosis in VFO patients with MSAP/SAP. To further study the possible mechanisms of effects of EEN on prognosis of AP, we measured serum level of CRP, IL-8, TNF-α, and IL-10 level in MSAP/SAP patients. Compared with VFO patients who received DEN, for VFO patients who received EEN, the serum levels of CRP (on the third and the seventh day after admission), the serum levels of TNF-α (on the third and the seventh day after admission), and IL-8 (on the third day after admission), respectively ($P < 0.05$). And the serum levels of IL-10 (on the seventh day after admission) increased significantly ($P < 0.05$). We also measured the serum level of I-FABP and citrulline in patients. EEN could decrease the serum level of I-FABP on the third and the seventh day after admission and increased the level of citrulline on the third and the seventh day after admission in VFO patients with MSAP/SAP after EEN when compared with those of VFO patients who received DEN, indicating that EEN may decrease the secondary pancreatic necrotic infection by protecting the intestinal mucosa. Our study suggested that EEN showed superiority over DEN in VFO patients with MSAP/SAP, mainly manifested by decreasing pancreatic necrotic infection, the mechanism of which might be related with inhibiting inflammation reactions and protecting intestinal mucosa from injury and ischemia.[37]

EEN can improve the prognosis of AP, but the optimal initiation time is still controversial. Previous studies believed that EEN initiated within 3 days could reduce the risk of secondary pancreatic infection and improve the nutritional

status of patients with AP, with a better tolerance. And it was believed that, if possible, EN should be initiated as soon as possible.[38] In our study, we initiated EEN within 48 hours after admission and all patients can tolerate EEN well, indicating that inition of EEN within 48 hours might be feasible and safe.

Regretfully, our study also found that EEN did not decrease the mortality of MSAP/SAP in VFO patients, which was not in accordance with previous studies,[11] but in accordance with one study published in NEJM,[12] in which study EEN did not show the superiority of early nasoenteric tube feeding, as compared with an oral diet after 72 hours, in reducing the rate of infection or death in patients with AP at high risk for complications. These findings do not support clinical guidelines recommending the early start of nasoenteric tube feeding in all patients with SAP to reduce the risks of infection and death. However, this trial was not powered to exclude a substantial benefit of early feeding regarding death rate. There are several possible explanations for the negative result of our study. (1) The main cause of death of obese patients in MSAP/SAP was respiratory failure, which explained why there is no difference of total death rate between group B and group C. (2) Previous trials showed an improved outcome after early nasoenteric tube feeding as compared with total PN. This may be explained in part by complications associated with providing total PN, such as catheter-related infections.[39] (3) A third explanation for the negative result may be that the study was too small to detect a difference between the 2 groups. To our knowledge, this is the largest trial of nutrition in patients with AP that has been performed so far, but the wide confidence interval for the primary endpoint may indicate that an even larger trial is needed.

Of course, our study has some limitations, we considered for the final analysis those patients with the admission after 48 hours, and we also included patients transferred from other hospitals, it may be biased because of difficulties with the assessment of the onset of symptoms before admission to hospital that has resulted in including, for the purposes of this analysis, the patients at different points in the development of the disease.

Further large multicenter prospective studies involving subjects from different demographics and regions are needed to properly validate our findings. In the present study, we did not investigate the effect of etiology on severity of AP because our aim was to identify effects of EEN on MSAP/SAP. With larger multicenter studies, it may be possible to risk-stratify patients as per etiology. Moreover, as this study did not base on a pathophysiological model, the precise mechanisms of EEN in AP patients should be verified by more basic experiments.

As the prevalence of obesity continues to increase worldwide, treatment of MSAP/SAP in obese patients remains a clinical challenge. It would be a far-reaching significance that EEN in VFO patients with MSAP/SAP in the early stage may prevent the development of MSAP/SAP by inhibiting the inflammatory cytokine pathway, adjusting the imbalance of inflammatory response, and alleviating ischemia of intestine mucosa.

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