Impact of body mass index on the incidence and severity of post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract	**Background** Pancreatitis is a potential major complication after endoscopic retrograde cholangiopancreatography (post-ERCP pancreatitis; PEP). Obesity has been associated with increased severity of acute pancreatitis. However, the correlation between obesity and PEP is controversial. Therefore, our study aimed to clarify the relationship between body mass index (BMI) and the incidence and severity of PEP. **Methods** A retrospective cohort study was conducted to elucidate the relationship between BMI and PEP in all patients who underwent ERCP in a tertiary referral center between January 2009 and October 2016. Patient characteristics and procedure details were collected. PEP was defined by consensus criteria. Multivariate logistic regression was used to determine the association between BMI and PEP. **Results** The analysis included 2236 patients whose BMI was recorded and had adequate follow up (921 with BMI≥30 kg/m^2, 1315 with BMI<30 kg/m^2). PEP was diagnosed in 107 (4.8%) patients. PEP was seen in 49 obese patients (5.3%) and 58 non-obese patients (4.4%). In the univariate and multivariate analysis BMI≥30 kg/m^2 was not associated with PEP (odds ratio 1.2, 95%CI 0.8-1.8; P=0.32). A subgroup analysis of different BMI subcategories found that BMI was not associated with the incidence or severity of PEP. **Conclusion** In the largest study to date, neither obesity nor low body weight increased the incidence or severity of PEP. **Keywords** Obesity, underweight, body mass index, post-ERCP pancreatitis *Ann Gastroenterol 2019; 32 (3): 298-302*

Introduction

Acute pancreatitis is a major complication after endoscopic retrograde cholangiopancreatography (ERCP). The incidence of post-ERCP pancreatitis (PEP) ranges from 1-9% in average-risk patients [1] and from 11-40% in high-risk patients, with a 0.1% mortality risk related to pancreatitis and an annual healthcare expenditure totaling $199 million in the United States [2-9].

Risk factors for PEP have been studied extensively and are classified into patient- and procedure-related factors. Procedure-related risk factors include difficult or failed biliary cannulation, biliary sphincter balloon dilatation, pancreatic sphincterotomy and pancreatic duct injection. Patient-related factors such as young age, female sex, suspected sphincter of Oddi dysfunction, history of recurrent pancreatitis, history of prior PEP, and absence of chronic pancreatitis have all been shown to increase the likelihood of PEP [10-13]. Identification of these risk factors has allowed clinicians to risk-stratify patients and determine if PEP prophylaxis is necessary.

Studies have shown that obesity may contribute to the incidence, severity and mortality of acute pancreatitis [14-17]. This is presumably due to the chronic low-grade inflammatory state that has been observed in obese patients [18]. Obesity is also associated with decreased levels of adiponectin, an anti-inflammatory adipokine that may be a protective factor

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for acute pancreatitis [19]. Additionally, peripancreatic and retroperitoneal fat deposits could be susceptible to fat necrosis and increase the risk of additional local complications of acute pancreatitis, such as abscesses and pseudocysts [15].

The correlation between obesity and the incidence and severity of PEP has not yet been elucidated. A larger retrospective study of 964 patients by Deenadayalu *et al* showed that rates of PEP did not differ between patients with a body mass index (BMI)≥30 kg/m² and those with BMI<30 kg/m² (12.5% vs. 16.4%, respectively, P=0.14).

In contrast, Cotton *et al* showed that obesity is associated with post-ERCP complications, including PEP [20]. To complicate things further, a recent retrospective study of 583 patients by Fujisawa *et al* demonstrated that obese patients (BMI≥30 kg/m²) had a significantly higher rate of PEP compared to overweight (BMI 25-30 kg/m²), normal-weight (BMI 18.5-25 kg/m²), and underweight (BMI<18.5 kg/m²) patients. However, one of the limitation of the Fujisawa *et al* study that only 20 patients were obese [21]. Furthermore, Kumar *et al* performed a national database analysis that was suggestive of a positive correlation between obesity and PEP (odds ratio [OR] 1.55, 95% confidence interval [CI] 1.25-1.92) [24].

While numerous studies have examined the relationship between obesity and acute pancreatitis, far less is known about low BMI and acute pancreatitis, let alone PEP. Fujisawa *et al* reported that underweight patients (BMI<18.5) had higher rates of PEP compared to normal-weight individuals (BMI 18.5-25). There was no difference in the severity of PEP between normal- and underweight patients [19]. In comparison, a study by Deenadayalu *et al* examined the incidence of PEP in patients with BMI<20 and found no increase in PEP [21]. In this study, we aimed to better clarify the relationship between BMI and the incidence and severity of PEP.

Patients and methods

After approval by the University and Medical Center Institutional Review Board at East Carolina University/ Vidant Medical Center, we conducted a retrospective study of all ERCPs performed at the Center from January 2009 to October 2016. The study included all patients who underwent diagnostic or therapeutic ERCP within the study period.

The procedures were performed by 4 experienced endoscopists. All patients underwent ERCP with a standard duodenoscope (JF 260 or 260V; Olympus Optical Co., Ltd., Tokyo, Japan). Patient characteristics and procedural details were collected. Patients noted to have had acute pancreatitis within 72 h before the procedure were excluded from the study.

We reviewed patient demographic information, relevant medical history and home medications. All available laboratory blood work, pre- and post-procedure imaging studies, and follow-up documentation were also reviewed. Procedure details, including sphincterotomy, biopsy, stent placement/ removal, cannulation of the common bile duct, cannulation of the main pancreatic duct, cholangiogram, and pancreatogram were noted. Type and size of any endobiliary stent were noted,

along with information on other interventions performed during the ERCP.

Follow up

All the documented complications of ERCP in the electronic health record from subsequent admissions, emergency room or follow-up clinic visits, nurse's post-procedure phone calls and notifications of admission to another hospital or emergency room were reviewed. Complications were collected, including post-ERCP pancreatitis, end-organ damage, pancreatic necrosis, and death.

Definitions

BMI was classified according to the World Health Organization's definition: underweight, BMI<18.5 kg/m²; normal weight, BMI 18.5-25 kg/m²; obese, BMI 30-40 kg/m²; morbidly obese, BMI≥40 kg/m².

PEP was defined as new-onset or worsening abdominal pain causing an unplanned admission following an outpatient ERCP, or prolongation of a hospital stay following an ERCP. This diagnosis was associated with an increase in serum lipase or amylase levels to at least 3-fold greater than normal approximately 24 h after the procedure [15].

The severity of PEP was graded according to the revised Atlanta classification: mild, no evidence of organ failure or local or systemic complications; moderate, transient organ failure, or local or systemic complications in the absence of persistent organ failure; or severe, persistent organ failure or pancreatic necrosis. High-risk ERCP was defined based on prospectively validated patient and procedure-related independent risk factors [16-20].

Outcomes

The primary outcome of interest was the incidence of PEP in consecutive ERCPs. The secondary outcome of interest was the severity of PEP.

Statistical analysis

Continuous variables were evaluated using Student's *t*-test and categorical variables using Fisher's exact test. Patients with BMI≥30 kg/m² were compared with those with BMI <30 kg/m². Univariate logistic regression analysis of clinical and procedural factors associated with PEP was then conducted, with PEP as the dependent variable and the following independent variables: age, sex, BMI, rectal indomethacin administration, procedure indication, bilirubin level, prior pancreatitis, prior PEP, cannulation of pancreatic duct with contrast, pancreatic or biliary sphincterotomy, difficult cannulation, brush/cytology, biopsy, stent placement, balloon dilation and stone extraction.

All mutually exclusive variables associated with PEP (P<0.1) in the univariate analysis were included in the multivariate logistic regression model. Statistical analysis was carried out using JMP software (v10; SAS Institute Inc., Cary, NC).

Results

A total of 2236 patients whose BMI was recorded and who had adequate follow up were included in the final analysis. The average patient age was 60±18 years; 1247 (56%) patients were female, and 991 (44%) were male. The average BMI was 29±8 (kg/m²). Procedure risk factors did not differ between the 2 groups.

Study outcome

Overall, 17% of the patients who underwent ERCP were high-risk for PEP. PEP was diagnosed in 107 (4.8%) patients. In total, 921 patients had BMI≥30 kg/m² while 1315 patients had BMI<30 kg/m². There was no statistically significant difference in the procedure or patients' risk factors between the patients in the low- (<30 kg/m²) and high-BMI (≥30 kg/m²) groups. Of the 921 patients with BMI≥30, 49 were diagnosed with PEP (5.3%). In comparison, 58 patients (4.4%) were diagnosed with PEP of the 1317 patients with BMI<30 kg/m² (odds ratio [OR] 1.2, 95%CI 0.82-1.8; P=0.32). There was no difference in the incidence of PEP in BMI subgroups (Fig. 1).

In the univariate analysis, the following factors were associated with PEP: female aged <40 years, biliary sphincterotomy, pancreatic sphincterotomy, cannulation of the main pancreatic duct, contrast injection into the pancreatic duct (limited and complete pancreatogram), difficult cannulation, failed pancreatic duct stent placement, and a history of recurrent acute pancreatitis (Table 1).

In the multivariate model, female sex and <40 years of age, biliary sphincterotomy, pancreatic sphincterotomy, contrast injection into the pancreatic duct (limited and complete pancreatogram), difficult cannulation, and failed pancreatic duct stent placement were associated with PEP. However, BMI≥30 did not impact the incidence of PEP (OR 1.1, 95%CI 0.75-1.8; P=0.48) (Table 2). Likewise, there was no difference in the incidence of PEP in the subgroup analysis of different BMI categories (Table 3).

Severity of PEP

Seven patients were diagnosed with moderately severe pancreatitis according to the revised Atlanta classification: one in the underweight group, two in the normal BMI group, three in the overweight group and one in the morbidly obese group.

Nine patients were diagnosed with severe pancreatitis: 1 in the underweight group, 2 in the normal BMI group, 1 in the overweight group, 3 in the obese group, and 2 in the morbidly obese group. Three of the 9 patients died within 30 days: 1 in the morbidly obese group, 1 in the obese group, and 1 in the normal BMI group.

Discussion

Results from our study indicated that increased BMI (≥30 kg/m²) does not increase the risk of PEP. Furthermore, different subcategories of BMI, including underweight, overweight, obese and morbidly obese, are not associated with a different incidence of PEP compared to normal-weight patients. Our results were consistent with those of Deenadayalu *et al* [21].

Likewise, our study clearly demonstrates that an increase or decrease in BMI does not impact the severity of PEP. We used the revised Atlanta classification to categorize the severity of PEP [22]. Persistent organ failure and necrosis were distributed equally between the obese and non-obese patients. Our results differ from observational studies that suggest obesity increases the incidence, severity, and mortality of acute pancreatitis [14-17]. This may be explained by differences
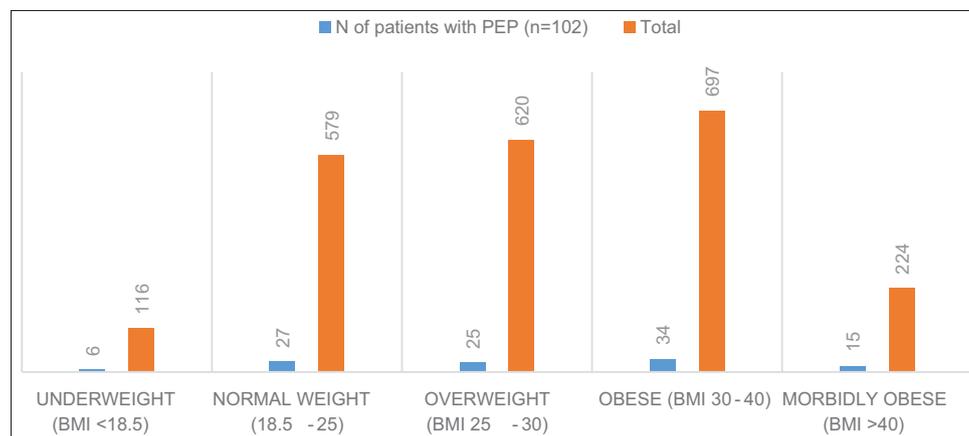
Figure 1 The number of PEP in each of the BMI subgroups
PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; BMI, body mass index

Table 1 Incidence of PEP according to risk factors

Risk factors	PEP n (%)	P	OR (95%CI)
Female sex	68/1246 (5.5)	0.09	0.7 (0.47-1.1)
Female <40 years	19/257 (7.4)	0.05*	1.7 (1.0-2.9)
Body mass index (BMI) ≥ 30	49/921 (5.3)	0.32	1.2 (0.8-1.8)
Normal bilirubin	51/1171 (4.4)	0.31	1.2 (0.8-1.8)
History of PEP	3/58 (5.2)	0.89	1.0 (0.3-3.5)
History of recurrent pancreatitis	11/121 (9)	0.002*	2.6 (1.3-5.1)
Difficult cannulation	48/500 (9.6)	0.0001*	5.6 (3.7-8.6)
Biliary sphincterotomy	74/1064 (7)	0.000*	2.5 (1.7-3.9)
Biliary stent insertion	41/787 (5.2)	0.49	1.2 (0.8-1.6)
Cannulation of MPD	57/658 (8.7)	0.000*	2.9 (2-4)
Cannulation of MPD with wire only	17/251 (6.7)	0.14	1.5 (0.9-2.6)
Limited pancreatogram	19/144 (13.2)	0.000*	3.5 (2.0-5.9)
Complete pancreatogram	20/197 (10.2)	0.001*	2.5 (1.5-4.2)
Pancreatic sphincterotomy	12/67 (18)	0.000*	4.8 (2.5-9.2)
Pancreatic duct dilatation	3/56 (5.4)	0.87	1.1 (0.34-3.6)
Failed PDS placement	8/17 (47)	0.0001*	19 (7.2-50)
EUS FNA of the pancreas	12/161 (7.5)	0.12	1.3 (0.9-3.1)

*P value <0.05

ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis; OR, odds ratio; CI, confidence interval; BMI, body mass index; MPD, main pancreatic duct; PDS, pancreatic duct stent; EUS FNA, endoscopic ultrasound fine-needle aspiration

Table 2 Factors associated with PEP, multivariate analysis

Factors	OR (95%CI)	P
Female <40 years	1.8 (1.0-3.1)	0.04*
Cannulation of pancreatic duct, limited pancreatogram	3.5 (1.8-6.0)	0.001*
Cannulation of pancreatic duct, complete pancreatogram	2.6 (1.3-4.8)	0.001*
Difficult cannulation	2.6 (1.7- 4)	0.001 *
Biliary sphincterotomy	3 (1.9-4.7)	0.001*
Pancreatic sphincterotomy	2.6 (1.1-5.6)	0.03*
Failed pancreatic duct stent placement	13 (4.0-41)	0.001*
Recurrent pancreatitis	1.4 (0.7-3)	0.29
BMI ≥30 kg/m²	1.2 (0.8-1.8)	0.49

*P<0.05

ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis; OR, odds ratio; CI, confidence interval; BMI, body mass index

Table 3 Incidence of PEP by BMI groups

BMI (kg/m²)	No. of patients with PEP (N=102)	RR (95%CI) P-value vs. normal weight
Underweight (BMI <18.5)	6/116 (4.6)	1 (0.4-2.6) P=0.8
Normal weight (18.5-25)	27/579 (4.7)	
Overweight (BMI 25-30)	25/620 (4)	0.9 (0.5-1.4) P=0.6
Obese (BMI 30-40)	34/697 (4.8)	1.0 (0.6-1.7) P=0.85
Morbidly obese (BMI >40)	15/224 (7)	1.4 (0.8-2.6) P=0.26

ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis; BMI, body mass index; RR, risk ratio; CI, confidence interval

(interleukin -1, -6, and -8) results in a systemic inflammatory response with multiorgan involvement [8,23].

There are several strengths to our study, including the large sample size. Given the relatively low incidence of PEP, a large sample size is imperative for the study to have enough power to detect differences in PEP between various BMI groups. To date, this is the largest retrospective study to investigate the relationship between PEP and BMI. Another strength of our study is the comprehensive dataset, which includes all possible confounders and the use of univariate and multivariate analyses to accurately define the impact of BMI on PEP.

The study has a few notable limitations. First, BMI was used as a surrogate for obesity. BMI is imperfect, as it uses weight rather than body composition and therefore cannot distinguish between adiposity and increased muscle mass. Second, while

in the etiology and mechanism of acute pancreatitis (such as alcohol or hypertryglyceridemia) and PEP. It has been suggested that local injury to the papilla from instrumentation, sphincterotomy or forceful and repetitive injection of contrast causes papillary edema or spasm. This is thought to result in ductal hypertension followed by reduced pancreatic duct drainage. The poor drainage initiates an inflammatory cascade, promoting intraluminal activation of proteolytic enzymes and autodigestion of the pancreas. Significant release of cytokines

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Summary Box

What is already known:

- Acute pancreatitis is a major complication following endoscopic retrograde cholangiopancreatography (ERCP)
- Procedure-related risk factors for post-ERCP pancreatitis (PEP) include difficult or failed biliary cannulation, biliary sphincter balloon dilatation, pancreatic sphincterotomy, and pancreatic duct injection
- Patient-related factors include young age, female sex, suspected sphincter of Oddi dysfunction, history of recurrent pancreatitis, history of prior PEP, and absence of chronic pancreatitis

What the new findings are:

- Obesity does not increase the incidence or severity of PEP
- Low body mass index does not impact the incidence or severity of PEP

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our study had a large sample size, it was retrospective in design and was thus susceptible to confounding. We attempted to adjust for this using univariate and multivariate analysis to detect any confounding variables.

In conclusion, our study showed no correlation between obesity and the incidence or severity of PEP. Likewise, patients classified as underweight did not have a higher incidence or severity of PEP. Future studies on this topic should ideally be performed prospectively to minimize bias and should use other measures of body composition to better evaluate obesity status.

References

1. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc* 2004;**59**:845-864.
2. Kochar B, Akshintala VS, Afghani E, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. *Gastrointest Endosc* 2015;**81**:143-149.
3. Wang AY, Strand DS, Shami VM. Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: medications and techniques. *Clin Gastroenterol Hepatol* 2016;**14**:1521-1532.
4. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007;**102**:1781-1788.
5. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996;**335**:909-918.
6. Freeman ML, DiSario JA, Nelson DB, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001;**54**:425-434.
7. Sherman S, Lehman GA. ERCP- and endoscopic sphincterotomy-induced pancreatitis. *Pancreas* 1991;**6**:350-367.
8. Sherman S, Ruffolo TA, Hawes RH, Lehman GA. Complications of endoscopic sphincterotomy. A prospective series with emphasis on the increased risk associated with sphincter of Oddi dysfunction and nondilated bile ducts. *Gastroenterology* 1991;**101**:1068-1075.
9. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991;**37**:383-393.
10. Andrade-Dávila VF, Chávez-Tostado M, Dávalos-Cobián C, et al. Rectal indomethacin versus placebo to reduce the incidence of pancreatitis after endoscopic retrograde cholangiopancreatography: results of a controlled clinical trial. *BMC Gastroenterol* 2015;**15**:85.
11. Elmunzer BJ, Scheiman JM, Lehman GA, et al; U.S. Cooperative for Outcomes Research in Endoscopy (USCORE). A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med* 2012;**366**:1414-1422.
12. Freeman ML. Pancreatic stents for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Clin Gastroenterol Hepatol* 2007;**5**:1354-1365.
13. Rustagi T, Jamidar PA. Endoscopic retrograde cholangiopancreatography (ERCP)-related adverse events: post-ERCP pancreatitis. *Gastrointest Endosc Clin N Am* 2015;**25**:107-121.
14. Abu Hilal M, Armstrong T. The impact of obesity on the course and outcome of acute pancreatitis. *Obes Surg* 2008;**18**:326-328.
15. Martínez J, Sánchez-Payá J, Palazón JM, Suazo-Barahona J, Robles-Díaz G, Pérez-Mateo M. Is obesity a risk factor in acute pancreatitis? A meta-analysis. *Pancreatology* 2004;**4**:42-48.
16. Hong S, Qiwen B, Ying J, Wei A, Chaoyang T. Body mass index and the risk and prognosis of acute pancreatitis: a meta-analysis. *Eur J Gastroenterol Hepatol* 2011;**23**:1136-1143.
17. Krishna SG, Hinton A, Oza V, et al. Morbid obesity is associated with adverse clinical outcomes in acute pancreatitis: a propensity-matched study. *Am J Gastroenterol* 2015;**110**:1608-1619.
18. Papachristou GI, Papachristou DJ, Avula H, Slivka A, Whitcomb DC. Obesity increases the severity of acute pancreatitis: performance of APACHE-O score and correlation with the inflammatory response. *Pancreatology* 2006;**6**:279-285.
19. Fujisawa T, Kagawa K, Hisatomi K, et al. Obesity with abundant subcutaneous adipose tissue increases the risk of post-ERCP pancreatitis. *J Gastroenterol* 2016;**51**:931-938.
20. Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009;**70**:80-88.
21. Deenadayalu VP, Blaut U, Watkins JL, et al. Does obesity confer an increased risk and/or more severe course of post-ERCP pancreatitis?: a retrospective, multicenter study. *J Clin Gastroenterol* 2008;**42**:1103-1109.
22. Banks PA, Bollen TL, Dervenis C, et al; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;**62**:102-111.
23. Pezzilli R, Romboli E, Campana D, Corinaldesi R. Mechanisms involved in the onset of post-ERCP pancreatitis. *JOP* 2002;**3**:162-168.
24. Kumar N, Gergi MA, Thompson CC. Obesity is an independent risk factor for post-ERCP pancreatitis: results of a nationwide database analysis. *Gastrointest Endosc* 2012;**75**:AB142.