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The impact of age on the incidence and severity of post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

Background With advancing age there is progressive pancreatic atrophy and fibrosis, leading to tissue destruction and chronic pancreatitis that has been found to be protective against post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). However, there are no reports regarding the potential effect of the aging pancreatic changes on the incidence and severity of PEP. Therefore, the aim of the present study was to investigate the impact of senile changes in the pancreas on the incidence and severity of PEP.

Methods A total of 2688 patients who underwent the first therapeutic ERCP at a single center were included in the final analysis of the study. Patients were classified into two groups: 1644 patients aged ≤75 years (mean age 61.56+1.26 years), group A; and 1044 patients aged >75 years (mean age 81.97+4.29 years), group B. Patients' files were identified using a retrospective database linked to the endoscopy reporting system. Patients' characteristic, endoscopic findings, details of intervention and rate and severity of PEP were evaluated.

Results No significant differences between the two groups were observed with regard to ERCP indication, patient- and technique-related risk factors for PEP, presence of periampullary diverticulum, and type of therapeutic intervention. The incidence of PEP was 5.2% in group A and 4% in group B (P=NS) with comparable grades of severity. All episodes of pancreatitis had full recovery with conventional treatment. One death occurred from respiratory arrest in each group of patients.

Conclusion This study shows that the pancreatic changes associated with aging do not influence the incidence and severity of PEP.

Keywords Endoscopic retrograde cholangiopancreatography, post-ERCP pancreatitis, age, elderly

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Conflict of Interest: None

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Introduction

According to the World Health Organization's 2013 statistics, life expectancy has increased globally. Likewise, life expectancy at age 60 in the United States increased from 21 to 23 years and a longer life expectancy is predicted, with a progressive increase in the elderly population [1]. The number of the elderly with biliary pathologies is also increasing, swelling the demand on medical services to provide care for these patients. Therefore, endoscopic retrograde cholangiopancreatography (ERCP) would be increasingly required in elderly patients. ERCP is less invasive than surgery, but is a highly effective procedure that has played a major role in the management of biliary and pancreatic diseases in patients of advanced age [2]. Therapeutic ERCP has become an almost exclusively endoscopic therapeutic procedure for biliary and pancreatic diseases and it is a potentially life-

saving intervention for the elderly population [3,4]. In this regard, post-ERCP pancreatitis (PEP) continues to be the most frequent and feared complication, with considerable morbidity and occasionally mortality, increasing health care costs by more than $150 million annually in the United States [3-5].

Enlargement of the main pancreatic duct, irregularities of the main pancreatic duct and side branches, lobular fibrosis and pancreatic lithiasis in small pancreatic ducts are abnormalities that increase linearly with the aging pancreas [6,7]. In this respect, it is generally believed that the generalized fibrosis and scarring, advanced duct alterations and calcifications observed in chronic pancreatitis have a protective role against the development of acute pancreatitis or reduce its severity [3,4,8]; moreover, differentiating pancreatic changes in the elderly from chronic pancreatitis might be difficult, particularly in the early stages, in terms of structural and functional changes [7].

Although many studies [2,4,8] have reported that therapeutic ERCP can be performed with safety in patients of advanced age, there are no reports regarding the potential effect of the aging pancreatic changes on the incidence and severity of PEP. Therefore, the aim of the present study was to investigate the impact of old age (>75 years) and its associated pancreatic changes on the clinical outcomes and adverse events following ERCP in terms of the incidence and severity of PEP.

Patients and methods

Data from patients who underwent therapeutic ERCP during the period January 2005 to December 2012, and were included in several studies, were retrospectively collected to determine the incidence and severity of PEP in two groups of patients: those ≤75 years old, group A; and those >75 years old, group B. A higher incidence of senile changes in pancreatic morphology has been observed in the latter group [6,7]. The data analyzed included demographics, clinical history, blood test results, procedural details, technical procedures, procedural findings, diagnosis and grade of severity of PEP. Patients were excluded from the study for any of the following reasons: previous sphincterotomy, chronic pancreatitis, ampullary or pancreatic cancer, because of the lower risk of PEP in new or chronic obstruction of the pancreatic duct. Permission to review the patients' data was granted by the hospital's Institutional Review Board.

ERCP procedure

Patients presented for the procedure at 08:00 am after a 12-h fast and remained fasting for at least 24 h after the procedure. Before ERCP, informed consent was obtained from each patient and/or caregiver. All procedures were performed by an experienced dedicated endoscopist (P.K.), who performs more than 400 ERCPs annually, using a standard therapeutic duodenoscope. During each session of ERCP, all the patients underwent continuous monitoring with pulse oximetry and electrocardiogram. Pharyngeal anesthesia was induced with a spray of 10% lidocaine (Xylocaine®; Astra Zeneca, Athens, Greece). Conscious sedation was administered only when the patient's condition was stable. For conscious sedation, intravenous injection of midazolam and pethidine was used at the discretion of the endoscopist. Hyoscine-n-butyl (Buscopan; Boehringer, Ingelheim Ltd., UK) or glucagon was given for duodenal relaxation if needed.

For ductal opacification, contrast medium (50% sodium meglumine amide triaroate diluted in distilled water) was injected manually, under fluoroscopic guidance. Pancreatograms were graded according to the extent of pancreatic opacification: main pancreatic duct, first and secondary class branches or acinarization.

Cannulation of the common bile duct (CBD) was firstly attempted with a sphincterotome (Clever-cut; Olympus, Athens). If the endoscopist failed to cannulate the CBD with the sphincterotome within 5 min, a hydrophilic guidewire (Jagwire or Dreamwire; Boston Scientific, Athens) was introduced for another 5 min. If the techniques failed, a precut access papillotomy was attempted; after catheterization of the CBD the procedure was completed with a standard sphincterotome. Endoscopic sphincterotomies were performed via a hydrophilic guidewire to achieve controlled cutting and avoid the "zipper cut" phenomenon. All endoscopic sphincterotomies were done using blended current (cut 45 W, coagulation 30 W) from an Olympus electrosurgical unit (PSD-30). The length of the endoscopic sphincterotomy depended on the indication: small for stent placement, or as large as possible for choledocholithiasis. It is not the senior endoscopist's (P.K.) policy to place pancreatic stents for PEP prophylaxis; therefore, pancreatic stents were not placed in any patient.

Data collected by the endoscopist conducting the procedures comprised the following: specific details concerning the procedure, including the presence of periampullary diverticulum; method of CBD cannulation (sphincterotome, sphincterotome plus hydrophilic guidewire); CBD diameter; type of precut papillotomy (conventional needle-knife papillotomy, suprapapillary fistulotomy or transpancreatic sphincterotomy); extent of pancreatic opacification; and type of therapy. Venous blood was drawn from each patient for serologic testing for amylase activity using an automated analyzer before the procedure and at 6 h post-procedure in all patients and at 24 h in hospitalized patients.

Definitions

Cannulation was considered difficult if more than 10 min were needed to achieve deep CBD cannulation using the sphincterotome, with or without the hydrophilic guidewire. The CBD diameter was the measured maximal duct diameter within 2 cm of the papilla, adjusted for radiographic magnification.

Sphincter of Oddi dysfunction (SOD) was defined according to the revised Milwaukee SOD classification system [9]. Biliary manometry was not performed.

The definition of PEP and the grading of its severity were based on consensus criteria [10]. PEP was diagnosed when new-onset or increased abdominal pain lasting more than 24 h caused an unplanned admission of an outpatient for more than one night or prolonged hospitalization of an inpatient and was associated with at least a threefold increase in serum amylase at approximately 6 or 24 h post-procedure. Specifically, PEP was graded as follows: (i) mild symptoms lasting 3 days, mildly edematous appearance of the pancreas by computed tomography (CT) scan, and hospitalization for 1-3 days after the procedure; (ii) moderate, requiring specific therapeutic measures for 4-10 days post-procedure (Balthazar's grade B/C on CT); and (iii) severe local or systemic complications lasting longer than 10 days post-treatment (Balthazar's grade D/E or death). CT findings that included the presence of either tissue necrosis involving >30% of the pancreatic gland or peripancreatic fluid accumulation were also grounds to classify the pancreatitis as severe.

Follow up

After the procedure, all patients were monitored in the ward with frequent, close and direct contact with the endoscopist who performed the ERCP to decide whether the patient could be discharged. Each patient and escorts were given detailed standardized written information about possible post-procedure complications and family doctors and local hospitals were also informed about the intervention. All were instructed to contact the on-call ERCP staff immediately, should any of the symptoms described arise. Finally, we suggested that the discharged patients fasted (except for water) until the following morning, at which time a clear liquid breakfast could be ingested and followed, if tolerated, by a regular diet. In addition, patients were followed up in an outpatient clinic or by telephone call on days 1, 10 and 30 post-ERCP, to detect any delayed complications.

Study outcomes

The primary study outcome was to investigate the influence of old age (>75 years) on the incidence and severity of PEP.

Statistical analysis

Categorical variables were analyzed using chi-square and Fisher's exact tests, as appropriate, while continuous variables were expressed as means with standard deviation (SD) and analyzed using the Student's *t*-test. Statistical significance was set at $P<0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 16.0, Chicago, IL, USA).

Results

During the study period, 2898 patients underwent therapeutic ERCP. Of these, 2688 were enrolled in the final analysis: 1186 men (44.12%) and 1502 women (55.88%). Two hundred ten patients were excluded because of insufficient data regarding the type of complication and details of the procedure.

Group A (age ≤75 years) included 1644 patients: 738 men (44.9%), 906 women (55.1%), mean age 61.56±1.26 years. Group B (age >75 years) included 1044 patients: 448 men (42.9%), 596 women (57.1%), mean age 81.97±4.29 years. The clinical characteristics of the patients are summarized in Table 1 and did not differ significantly between the two groups, except for the history of coronary artery disease/heart failure ($P=0.012$), chronic obstructive pulmonary disease ($P=0.007$), previous stroke ($P=0.026$), and the use of aspirin/clopidogrel ($P=0.01$) or anticoagulants ($P=0.03$), which were statistically more frequent in patients with age >75 years (group B).

The main indication for therapeutic ERCP was choledocholithiasis, followed by biliary cancer (Table 1). Details of the endoscopic findings and the treatment performed in the two groups are described in Table 2. The presence of periampullary diverticulum was similar in both groups. There was no significant difference between the groups in regard to the rate of opacification of the main pancreatic duct, first and second class pancreatic ductules, or acinarization of the pancreas (Table 2). No difference was observed in the number of difficult cannulations, or the precut access papillotomy and its subtypes (needle knife, suprapapillary fistulotomy and transpancreatic sphincterotomy) (Table 2). Moreover, there was no difference between the studied groups in regard to the rate of endoscopic sphincterotomy plus extraction of stones with basket or balloon, mechanical lithotripsy, or the placement of plastic or metal stents (Table 2).

The overall rate of PEP was (4.76%) (128 patients); PEP occurred in 86 patients (5.2%) of group A and 42 patients (4%) of group B. It was mild, moderate and severe in 70 (4.3%), 10 (0.6%) and 5 patients (0.3%) of group A, and in 28 (2.8%), 9 (0.9%) and 4 patients (0.4%) of group B, respectively (Table 3). One death occurred from respiratory failure in each group (Table 3).

Discussion

The age of the general population in the western world is increasing, with a significant proportion reaching advanced age; this phenomenon is considered to be the result of improvements in medical care, including progress in pharmaceutical and biomedical technology [11]. With aging of the population, the occurrence of pancreaticobiliary diseases is also increasing [12]. Pancreatobiliary tract diseases, including choledocholithiasis, are commonly encountered in the elderly [13] and bile duct stone-related adverse events have significant morbidity in elderly patients because of the high prevalence of comorbidities such as

Table 1 Characteristics of the patients

Characteristic	n (%)		P
	Patients aged ≤75 years	Patients aged >75 years	
No of patients	1644	1044	
Sex (male/female)	738/906 (44.9/55.1)	448/596 (42.9/57.1)	NS
Age (mean±SD) (years)	61.56±1.26	81.97±4.29	
Prior cholecystectomy	1113 (67.7)	634 (60.7)	NS
Indication for ERCP			
Choledocholithiasis	1286 (77.1)	859 (82.3)	NS
History of acute pancreatitis	65 (4.0)	19 (1.8)	NS
Biliary cancer	151 (9.2)	115 (11.0)	NS
Bile duct leak	59 (3.6)	10 (1.0)	NS
Benign biliary stricture	25 (1.5)	15 (1.4)	NS
SOD	62 (3.8)	17 (1.6)	NS
Other	14 (0.9)	9 (0.9)	NS
Comorbid associated diseases			
Hypertension	372 (22.6)	243 (23.3)	NS
Coronary artery disease/heart failure	161 (9.8)	190 (18.2)	0.012
Chronic obstructive pulmonary disease	47 (2.9)	65 (6.2)	0.007
Previous stroke	32 (1.9)	56 (5.4)	0.026
Drugs			
Aspirin/clopidogrel	138 (8.4)	184 (17.6)	0.01
NSAIDs	85 (5.2)	32 (3.1)	NS
Anticoagulants	27 (1.6)	29 (2.8)	0.03

ERCP, endoscopic retrograde cholangiopancreatography; SOD, sphincter of Oddi dysfunction; NSAIDs, non-steroidal anti-inflammatory drugs

chronic obstructive pulmonary disease, cardiovascular disorders and cerebrovascular accidents. In particular, the elderly are susceptible to procedure-associated infections, such as cholangitis or cholecystitis, due to the compromised innate and adaptive immune systems; this may largely explain the higher rates of morbidity and mortality in the elderly [14-16]. However, surgery in elderly patients carries higher complication and mortality rates when compared to the younger patient. For such elderly patients, who frequently present with the aforementioned concomitant comorbid conditions and a poor American Society of Anesthesiologists score, the mortality rate after abdominal surgery has been reported to be up to 21%. In consequence, the need for endoscopic intervention is increasing [11]; ERCP is favored as a useful alternative for urgent and/or inoperable situations in elderly patients.

Some studies have examined the safety of therapeutic ERCP in elderly patients and demonstrated that there is no statistically significant difference towards a higher complication rate in elderly patients, despite their higher comorbidity [17-19]. In this regard, the present study shows that the aging pancreatic changes do not influence the incidence and severity of PEP. It is important to note that this study differs from previous studies, because it is the largest to focus exclusively on the impact of old age on PEP; furthermore, all procedures were performed by an experienced pancreatobiliary endoscopist in a single tertiary referral center, thus eliminating the contribution of the endoscopist's experience, a main risk factor for PEP development.

PEP continues to remain the most common and severe post-ERCP complication, with rates ranging between 2% and 9% [3,4]. Despite the improvements in training in ERCP, and the introduction in recent years of accessories (hydrophilic guidewires, steerable catheters, electrosurgical units with microprocessors) that have facilitated the cannulation of the desired duct and minimized the trauma to the major papilla, a significant risk factor for PEP, this complication currently accounts for substantial annual morbidity and healthcare expenditure, and occasional death [20].

In the present series, the incidence of PEP was 4% in the elderly and 5.2% in the younger group (Table 3), consistent with previous studies [17-19]; moreover, despite the higher prevalence of comorbidity in the elderly group, the severity of PEP was comparable to that observed in younger patients. Remarkably, in the well-recognized patient- (female sex, history of acute pancreatitis, SOD) and procedure-related (pancreatic opacification, precut access papillotomy) risk factors, no difference was found between the two groups. In

Table 2 Details of therapeutic ERCP

Detail of ERCP	n (%)		P
	Patients aged ≤75 years	Patients aged >75 years	
Presence of periampullary diverticulum	332 (20.2)	196 (18.8)	NS
Pancreas opacification	327 (19.9)	169 (16.2)	NS
Main pancreatic duct	187 (11.4)	86 (8.2)	NS
First and second class branches	127 (7.7)	76 (7.3)	NS
Acinarization	13 (0.8)	7 (0.7)	NS
Difficult cannulation	621 (37.9)	441 (42.2)	NS
Conventional ES	1459 (88.7)	857 (82.1)	NS
Precut access papillotomy	185 (11.3)	187 (17.9)	NS
Needle knife	93 (5.7)	79 (7.6)	NS
Suprapapillary fistulotomy	48 (2.9)	54 (5.2)	NS
Transpancreatic	44 (2.7)	54 (5.2)	NS
ES plus extraction of stones with basket or balloon	970 (59)	581 (55.6)	NS
Mechanical lithotripsy	347 (21.1)	229 (21.9)	NS
Stent placement	82 (5.0)	68 (6.5)	NS
Metal stent	22 (1.3)	20 (1.9)	NS

ES, endoscopic sphincterotomy; ERCP, endoscopic retrograde cholangiopancreatography

Table 3 Incidence of post-ERCP pancre atitis

	Patientswith age ≤75 years	Patients with age >75 years	p
Pancer atitis	86 (5.2)	42 (4.0)	NS
Mild	71 (4.3)	29 (2.8)	NS
Moderate	10 (0.6)	9 (0.9)	NS
Sever	5 (0.3)	4 (0.4)	NS
Death	1 (0.06)	1 (0.1)	NS

our study we used 75 years as cutoff for the old-age group, because most authors [6,7] consider that over this age the senile changes in the pancreas (enlargement, irregularities of the main pancreatic duct and side branches, the presence of small cysts and pancreatolithiasis) are observed [21-23].

Some authors [18] described a lower rate of PEP, though with no statistically significant difference, in the elderly patients who had a mild post-procedure course; they explained their findings by the progressive decline in pancreatic exocrine function with aging that might protect older patients from injury. A growing body of research [8,21-24] has examined the structural and physiologic changes in the normal pancreas that occur with advancing age and showed contradictory results. The disparity in the results may be explained in part by the different methodologies employed in the various studies or the inadvertent inclusion of patients with asymptomatic pancreatic disease. However, most investigators [8,21,24] agree that a form of chronic pancreatitis may occur in elderly patients in the absence of symptoms, including abdominal pain. The cause of these senile changes in the pancreas remain unclear, though atherosclerosis has been proposed as a risk factor and/or genetic susceptibility is involved [11]; however, the question remains whether these senile changes in the pancreas are clinically important.

Summary Box

What is already known:

- Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) has become an almost exclusively endoscopic therapeutic procedure for biliary and pancreatic diseases and it is a potentially life-saving and safe intervention in the elderly population
- Enlargement of the main pancreatic duct, irregularities of the main pancreatic duct and side branches, lobular fibrosis and pancreatic lithiasis in small pancreatic ducts are abnormalities that increase linearly with the aging pancreas
- Chronic pancreatitis alterations have a protective role against acute pancreatitis development or can reduce the severity of post-ERCP pancreatitis (PEP)

What the new findings are:

- The aging pancreatic changes do not influence the incidence and severity of PEP

The strength of the present study is the large sample size, which increases the power of the statistical analysis. The principal limitations are: i) the data were collected retrospectively; ii) the results cannot be generalized, as our institution is a tertiary referral center and all ERCPs were performed by a single experienced dedicated endoscopist who performs at least 10 therapeutic ERCPs per week, uncommon practice for an average endoscopist.

In conclusion, senile pancreatic changes do not seem to influence the rate and severity of PEP. The decision to proceed with therapeutic ERCP must be taken based on its merit, not only on old age and its associated comorbidities.

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