Biomedicine Hub

Research Article

Biomed Hub 2021;6:111–117
DOI: 10.1159/000519826

Received: July 18, 2021
Accepted: September 22, 2021
Published online: November 1, 2021

Prevalence of Chronic Metabolic Comorbidities in Acute Pancreatitis and Its Impact on Early Gastrointestinal Symptoms during Hospitalization: A Prospective Cohort Study

Rachel Goodger Kanageswari Singaram Maxim S. Petrov

School of Medicine, University of Auckland, Auckland, New Zealand

Keywords

Acute pancreatitis · Diabetes mellitus · Obesity · Metabolic syndrome · Gastrointestinal symptoms · Patient-reported outcomes

Abstract

Background: The prevalence of chronic comorbidities is increasing worldwide, and this has been paralleled by a growing interest in how these comorbidities affect patients with acute pancreatitis. The aim was to investigate the associations between pre-existing diabetes mellitus, obesity, metabolic syndrome, and gastrointestinal symptoms during the early course of acute pancreatitis. ***Methods:*** This was a prospective cohort study of patients with a primary diagnosis of acute pancreatitis. Study groups were formed based on the presence of metabolic comorbidities (pre-existing diabetes mellitus, obesity, and metabolic syndrome). Patient-reported outcomes (nausea, bloating, and abdominal pain) were collected prospectively every 24 h (including weekends and public holidays) over the first 72 h of hospitalization. ***Results:*** A total of 183 consecutive patients were enrolled. Of them, 111 (61%) had at least one major metabolic comorbidity. Patients with pre-existing diabetes mellitus and those with metabolic syndrome had worse nausea at 49–72 h of hospitalization ($p = 0.017$ and $p = 0.012$, respectively), but not at other time points. Bloating and abdominal pain did not differ between the study groupings throughout the study period. The studied patient-reported outcomes did not differ significantly between acute pancreatitis patients with and without obesity at any point in time. ***Conclusion:*** More than 3 out of 5 patients hospitalized for acute pancreatitis have at least one major chronic metabolic comorbidity. The presence of metabolic comorbidities does not considerably and consistently affect early gastrointestinal symptoms in patients with acute pancreatitis.

Introduction

The prevalence of chronic metabolic comorbidities (such as diabetes mellitus, obesity, and metabolic syndrome) has been increasing relentlessly worldwide [1, 2]. At the same time, the incidence of acute pancreatitis (AP) – one of the most common acute gastrointestinal diseases – is projected to markedly increase by 2050 [3–5]. Numerous studies have shown that the above comorbidities have an impact on "hard" clinical outcomes during the course of AP such as mortality, ICU admission, and severity of AP [6–13].

R.G. and K.S. contributed equally to this work.

karger@karger.com
www.karger.com/bmh

Correspondence to:
Maxim S. Petrov, max.petrov@gmail.com

By contrast, "soft" clinical outcomes (such as patient-reported outcomes) have received only little attention in the AP setting [14, 15]. Given that the gastrointestinal system is one of the most affected organ systems during the course of AP and taking into account that there are no readily available instrumental methods to monitor gastrointestinal function during AP [16–20], consideration of patient-reported outcomes focused on gastrointestinal symptoms is conceptually appealing. However, there is a paucity of studies on these outcomes in the AP setting. Furthermore, the associations between chronic metabolic comorbidities and gastrointestinal symptoms in AP have not previously been investigated [21].

The primary aim was to determine the prevalence of chronic metabolic comorbidities in a prospective cohort of consecutive patients with AP. The secondary aim was to investigate whether these comorbidities affect gastrointestinal symptoms in patients with AP.

Table 1. Patient characteristics

	N = 183
Age, years[1]	49 (36–68)
Sex, *n* (%)	
Men	90 (49.2)
Women	93 (50.8)
Ethnicity, *n* (%)	
European	102 (55.7)
Maori/Pacific Islander	40 (21.9)
Others	41 (22.4)
Aetiology, *n* (%)	
Alcohol-related	44 (24.0)
Biliary	84 (45.9)
Others	55 (30.1)
Severity	
APACHE II score[1]	5.0 (3–12)
Metabolic comorbidities, *n* (%)	
Diabetes mellitus	22 (12)
Obesity	48 (26)
Metabolic syndrome	102 (56)

APACHE II, acute physiology and chronic health evaluation II.
[1] Data are presented as median (interquartile range).

Methods

Study Design

The study was a prospective cohort study conducted at Auckland City Hospital (New Zealand) as part of the PICTOR project. Patients were included in the study if they had a diagnosis of AP, were at least 18 years of age, and gave informed consent. Diagnosis of AP required at least 2 of the following 3 criteria to be met:

- Abdominal pain suggestive of AP;
- Serum amylase and/or pancreatic amylase and/or lipase at least 3 times the upper limit of normal (i.e., amylase ≥405 IU/L, pancreatic amylase ≥159 IU/L, and lipase ≥231 IU/L);
- Characteristic findings of AP on computed tomography (e.g., diffuse or segmental enlargement of the pancreas and/or peripancreatic necrosis and/or pancreatic necrosis).

Patients were excluded from the study if they had/were

- Chronic pancreatitis
- More than 96 h after onset of symptoms
- Post-endoscopic retrograde cholangiopancreatography pancreatitis
- Intraoperative diagnosis
- Pregnant or postpartum
- Malignancy
- Non-English speakers
- Cognitive impairment.

All patients were managed according to the standardized AP clinical care protocol [22].

Study Groups

Study groups were formed based on the following 3 comorbidities: pre-existing diabetes mellitus, obesity, and metabolic syndrome. Pre-existing diabetes mellitus was defined as documented fasting plasma glucose ≥7.0 mmol/L and/or glycated haemoglobin ≥48 mmol/mol and/or treatment with antidiabetic medications prior to hospitalization for AP. Obesity was defined by BMI (kg/m^2) according to the cutoff points recommended by the World Health Organization: normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Patients with a lower than normal BMI were excluded from the analysis. Weight and height were measured in the phase of convalescence in the present study (typically, 2 days prior to expected hospital discharge). Metabolic syndrome was defined according to the International Diabetes Federation definition [23]. This included central obesity (waist circumference ≥94 cm for European men and ≥80 cm for European women, with ethnicity-specific values for other ethnic groups) and at least 2 of the following 4 criteria: raised plasma fasting glucose (fasting plasma glucose ≥5.5 mmol/L or previously diagnosed type 2 diabetes mellitus), raised serum triglyceride level (triglyceride ≥1.7 mmol/L or specific treatment for dyslipidaemia), reduced high-density lipoprotein cholesterol (high-density lipoprotein cholesterol <1.04 mmol/L for men and <1.30 mmol/L for women), or arterial hypertension (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or treatment of previously diagnosed hypertension) [23].

Endpoints

The study endpoints were nausea, abdominal pain, and bloating. For all recruited patients, the above endpoints were monitored every 24 h (including weekends and public holidays) for 72 h using a purposely designed AP diary. The response to each question was recorded on a Likert scale of 0–10 (0 – not at all and 10 – most severe) in the AP diary.

Statistical Analysis

Data were analysed using SPSS Statistics for Windows version 25 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to determine the normality of distribution of continuous variables. Where appropriate, the non-parametric Kruskal-Wallis H test, the

Table 2. The relationship between metabolic comorbidities and gastrointestinal symptoms in the first 72 h of hospitalization for acute pancreatitis

Time period	Symptom	Adiposity				Diabetes mellitus			Metabolic syndrome		
		normal	overweight	obese	*p* value	present	absent	*p* value	present	absent	*p* value
0–24 h	Nausea	6.0 (0.0, 9.0)	4.5 (1.0, 7.0)	5.0 (0.0, 7.0)	0.202	5.0 (1.0, 8.0)	5.0 (0.0, 8.0)	0.796	5.0 (0.0, 8.0)	3.0 (0.0, 8.0)	0.507
	Abdominal pain	9.0 (7.0, 10.0)	8.0 (6.0, 9.8)	8.0 (7.0, 10.0)	0.489	9.0 (7.5, 10.0)	8.0 (6.8, 10.0)	0.163	8.0 (7.0, 9.5)	8.0 (5.0, 8.0)	0.135
	Bloating	3.5 (0.0, 7.0)	5.0 (0.8, 7.0)	5.0 (0.0, 7.0)	0.407	4.5 (0.0, 5.3)	5.0 (0.0, 7.0)	0.219	5.0 (0.0, 7.0)	5.0 (0.0, 7.0)	0.890
25–48 h	Nausea	2.0 (0.0, 7.0)	2.0 (0.0, 5.0)	0.5 (0.0, 3.0)	0.265	3.0 (0.0, 8.0)	1.0 (0.0, 5.0)	0.163	1.5 (0.0, 5.0)	0.0 (0.0, 1.5)	0.163
	Abdominal pain	4.5 (2.0, 6.8)	5.0 (2.8, 7.3)	5.0 (2.0, 7.0)	0.496	6.0 (2.3, 8.0)	5.0 (2.0, 7.0)	0.409	6.0 (2.3, 8.0)	5.0 (2.0, 7.0)	0.409
	Bloating	3.0 (0.0, 5.5)	4.0 (0.5, 6.0)	3.0 (0.0, 5.0)	0.275	2.5 (0.0, 6.5)	3.0 (0.0, 5.3)	0.679	2.5 (0.0, 6.5)	3.0 (0.0, 5.3)	0.679
49–72 h	Nausea	0.0 (0.0, 4.0)	0.5 (0.0, 3.5)	0.0 (0.0, 2.5)	0.405	2.5 (0.3, 6.5)	0.0 (0.0, 3.0)	0.017*	2.0 (0.0, 5.0)	0.0 (0.0, 0.0)	0.012*
	Abdominal pain	3.0 (1.0, 6.0)	4.5 (3.0, 7.0)	5.0 (2.0, 6.0)	0.230	5.0 (2.5, 8.0)	4.0 (2.0, 6.0)	0.376	5.0 (2.0, 7.0)	3.0 (1.5, 4.5)	0.074
	Bloating	1.5 (0.0, 5.8)	4.0 (0.3, 5.0)	2.0 (0.0, 5.0)	0.377	3.0 (0.0, 5.5)	3.0 (0.0, 5.0)	0.848	4.0 (0.0, 6.0)	3.0 (1.5, 5.0)	0.931

Data are presented as median (interquartile range). * $p < 0.05$.

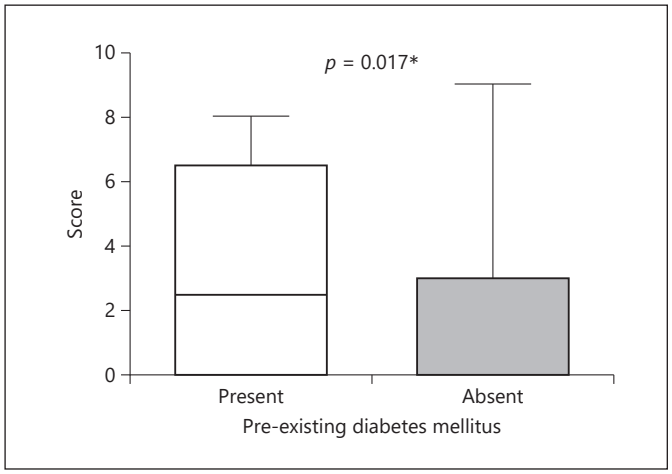

Fig. 1. Nausea scores at 49–72 h after hospitalization in acute pancreatitis patients with and without pre-existing diabetes mellitus.

χ^2 test, and the Fisher's exact test were conducted. The potential confounding factors were then analysed using the Kruskal-Wallis H test to investigate their individual effect on each study outcome. All continuous data were presented as median and interquartile range (twenty-fifth and seventy-fifth percentiles). All categorical data were presented as absolute and relative frequencies. In all analyses, *p* values <0.05 were accepted as statistically significant.

Results

Characteristics of the Cohort

A total of 183 consecutive patients with AP met the study eligibility criteria. These patients were admitted to the hospital in 12 (interquartile range 6–30) hours after onset of symptoms. Other characteristics are presented in Table 1. A total of 48 (26%) patients were obese, 22 (12%) patients had pre-existing diabetes mellitus, and 102 (56%) had metabolic syndrome. Overall, 111 (61%) patients in the study cohort had at least one major chronic metabolic comorbidity (obesity, pre-existing diabetes mellitus, or metabolic syndrome) at the time of hospitalization.

Pre-Existing Diabetes Mellitus

Comparison of baseline characteristics revealed a significant difference in age and APACHE II score between patients with and without pre-existing diabetes mellitus. The median age of those with and without pre-existing diabetes mellitus was 62 and 47 years, respectively (p = 0.010). The median APACHE II scores of those with and without pre-existing DM were 9 and 5, respectively (p = 0.002). There were no differences between the groupings in terms of sex and ethnicity. The nausea score at 49–72 h of hospitalization differed significantly (p = 0.017) between patients with pre-existing DM and those without it (Fig. 1). There were no significant differences between the groupings at 0–24 and 25–48 h of hospitalization. Abdominal pain and bloating did not differ between the study groupings throughout the study period (Table 2).

Obesity

Comparison of baseline characteristics revealed a significant difference in terms of ethnicity between the BMI categories. Patients of the Maori/Pacific Island origin had a greater prevalence of obesity (58%) compared with those of European or other origin (17% and 20%, respec-

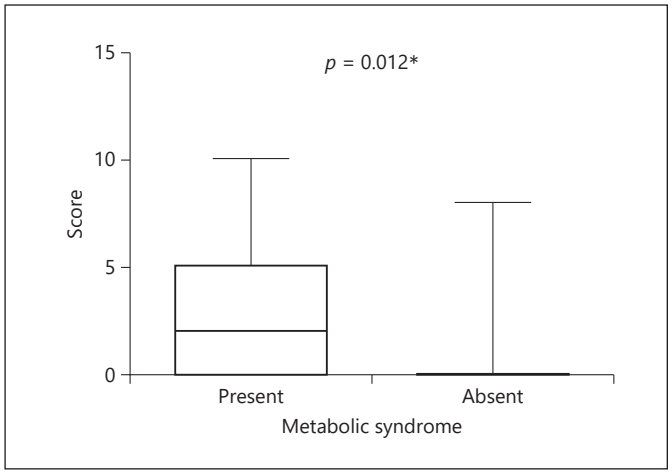

Fig. 2. Nausea scores at 49–72 h after hospitalization in acute pancreatitis patients with and without metabolic syndrome.

tively) ($p < 0.001$). There were no significant differences between the groupings in terms of age, sex, and APACHE II score. There were no significant differences between the groupings at 0–24, 25–48, and 49–72 h of hospitalization (Table 2).

Metabolic Syndrome

Comparison of baseline characteristics revealed a significant difference in terms of age between patients with and without metabolic syndrome. The median ages of those with and without metabolic syndrome were 50 and 37 years, respectively ($p = 0.003$). There were no differences between the groups in terms of sex, ethnicity, and APACHE II score. The nausea score at 49–72 h of hospitalization differed significantly ($p = 0.012$) between patients with metabolic syndrome and those without (Fig. 2). For the abdominal pain score, the prespecified threshold for statistical significance was just missed ($p = 0.074$) (Table 2). The bloating score did not differ significantly between the groupings at 49–72 h of hospitalization. There were no significant differences between the groupings at 0–24 and 25–48 h of hospitalization (Table 2).

Discussion

This was the first prospective cohort study to explore the relationship between pre-existing chronic metabolic comorbidities and gastrointestinal symptoms in patients with AP. One novel aspect of the present study is that it investigated in a prospective fashion not a single comorbidity but a suite of chronic metabolic comorbidities and showed that more than 3 out of 5 patients hospitalized for AP have at least one major chronic metabolic comorbidity at the time of hospitalization. This high prevalence of chronic metabolic comorbidities did not translate into a high incidence of hypertriglyceridaemia-induced pancreatitis as only 4 (2.2%) patients in out cohort had serum triglyceride levels of >1,000 mg/dL. The prevalence of individual comorbidities identified in the present prospective cohort study was broadly in agreement with previously published studies. In the present study, the prevalence of pre-existing diabetes mellitus was 12%, which is similar to the findings from a retrospective cohort study from Japan that found that 11% of AP patients had pre-existing diabetes mellitus [24]. Some other retrospective studies reported slightly higher prevalence of pre-existing diabetes mellitus in AP patients: 18% in a cohort study from Pennsylvania [12], 17% in a cohort study from California [25], and 19% in a cohort study from Taiwan [11]. In the present study, 26% of patients with AP were obese, which is in agreement with previously published prospective cohort studies: a prevalence of 24% in a study from India and 22% in a study from Belgium (all consistently using the same threshold of BMI ≥30 kg/m^2 to define obesity) [6, 10]. The present study also found that 56% of patients with AP fulfilled the criteria for metabolic syndrome using the International Diabetes Federation definition, which is consistent with the findings of a prospective cohort study from Saudi Arabia demonstrating that 63% of AP patients met the same criteria [13].

Another novel finding of this clinical study is that patients with pre-existing diabetes mellitus and/or metabolic syndrome were significantly associated with worse nausea at 49–72 h of hospitalization, when compared with patients who did not have these comorbidities. Although the effect of pre-existing diabetes mellitus on gastrointestinal symptoms in patients with AP has not previously been investigated, the association between diabetes mellitus and gastrointestinal symptoms is well established [26]. A large population-based study of 15,000 adults showed that diabetes mellitus (when compared with health) was associated with an increased prevalence of upper and lower gastrointestinal symptoms such as nausea, abdominal distension, and gastroesophageal reflux [27]. A smaller study found that the prevalence of gastrointestinal symptoms such as diarrhoea ($p = 0.030$) and bloating ($p = 0.038$) was greater in patients with long-standing type 2 diabetes mellitus com-

pared with controls without diabetes [28]. However, unlike in the present study, no significant difference was observed for nausea and vomiting between individuals with and without pre-existing diabetes mellitus (p = 0.267) [28]. This may be attributed to the difference in the study populations: acute setting patients hospitalized for AP versus community-based individuals with diabetes mellitus [28]. It is conceivable that more severe nausea in patients with AP who had pre-existing diabetes mellitus may be attributed to delayed gastric emptying, similar to that seen in diabetic patients [29, 30]. However, whether or not the reported observation is due to diabetic gastroparesis cannot be concluded from the present study as no significant differences were observed in terms of other gastrointestinal symptoms (such as abdominal pain or bloating), and gastrointestinal motility was not measured in the present study. Furthermore, a type II error cannot be ruled out.

This study had several limitations that need to be acknowledged. The study population was limited to patients recruited from a single hospital. A multicentre study may provide more robust and accurate estimates of the relationship between various comorbidities and gastrointestinal symptoms in patients with AP. In particular, the present study included only a few patients with necrotizing pancreatitis (n = 12), and therefore it was not positioned well to investigate the studied associations in this specific subgroup of patients. Also, APACHE II scores were only significantly different in patients with diabetes (but not other metabolic comorbidities), possibly reflecting the predominantly mild course of AP in the study cohort. The non-normal distribution of the data meant that a non-parametric statistical analysis was chosen (as opposed to a parametric statistical test). A limitation of all non-parametric tests is that it is challenging to undertake flexible modelling (such as accounting for possible confounders). This was partially overcome by summarizing all possible confounders individually after each Kruskal-Wallis test. The findings in the present study were based on patient-reported assessment of gastrointestinal symptoms, and the results might have been influenced by patient misinterpretation at the time of assessment. This effect was mitigated by members of the research team explaining and recording the results of the questionnaire in person in the daily diary; therefore, patient misunderstanding would have had a minimal impact on the results. Furthermore, patients with a cognitive impairment and non-English speakers were excluded from the study a priori to minimize patient misinterpretation of the questionnaire. Also, the questionnaire used to assess gastrointestinal symptoms has not been previously validated. However, the usefulness and validity of a Likert scale for investigating similar outcomes such as gastrointestinal motility has been shown to be reliable and valid. Patient-reported symptoms and health outcomes are an important part of clinical studies, and the Likert scale is simple, intuitive, and easy to interpret by patients and researchers alike.

Conclusion

The present prospective cohort study found that 61% of patients with AP have at least one chronic metabolic comorbidity at the time of hospitalization. The presence of chronic metabolic comorbidities in the majority of AP patients highlights the complexity of AP care required, which may involve not only surgeons and gastroenterologists but also other healthcare professionals [5]. It is important that future research is focused on developing a better understanding of how metabolic comorbidities, alone or combined, affect clinical outcomes in patients with AP and the risk of new-onset metabolic sequelae of AP that develop after hospital discharge [31–36].

Acknowledgment

This study was part of the Clinical and epidemiOlogical inveStigations in Metabolism, nutritiOn, and pancreatic diseaseS (COSMOS) program.

Statement of Ethics

The study was approved by the Health and Disability Ethics Committee (NTX/12/06/051). All participants provided their written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest.

Funding Sources

This study was supported by the Health Research Council of New Zealand (grant 15/035 to Professor Max Petrov), which played no role in the study design; collection, analysis, or interpretation of data; or writing of the manuscript.

Author Contributions

M.S.P. contributed to conceptualization and study design. R.G. and K.S. contributed to patient recruitment. R.G. and K.S. contributed to data acquisition. R.G. and K.S. contributed to analysis and interpretation of data. R.G. and K.S. contributed to statistical analysis. R.G. and K.S. drafted the manuscript. M.S.P. contributed to study supervision.

Data Availability Statement

All data generated or analysed during this study are included in this manuscript.

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