Pancreatology 19 (2019) 922–928

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Pancreatic calcifications associate with diverse aetiological risk factors in patients with chronic pancreatitis: A multicentre study of 1500 cases

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ARTICLE INFO

Article history:
Received 3 June 2019
Received in revised form
8 August 2019
Accepted 19 August 2019
Available online 21 August 2019

Keywords:
Chronic pancreatitis
Calcifications
Smoking
Alcohol
Endoscopy
Surgery

ABSTRACT

Background: Pancreatic calcifications is a common finding in patients with chronic pancreatitis (CP), but the underlying pathophysiology is incompletely understood. Past studies for risk factors of calcifications have generally been focused on single parameters or limited by small sample sizes. The aim of this study was to explore several patient and disease characteristics and their associations with pancreatic calcifications in a large cohort of CP patients with diverse aetiological risk factors.

Methods: This was a multicentre, cross-sectional study including 1509 patients with CP. Patient and disease characteristics were compared for patients with calcifications (n = 912) vs. without calcifications (n = 597). Multivariable logistic regression was performed to assess the parameters independently associated with calcifications.

Results: The mean age of patients was 53.9 ± 14.5 years and 1006 (67%) were men. The prevalence of calcifications was 60.4% in the overall patient cohort, but highly variable between patients with different aetiological risk factors (range: 2–69%). On multivariate analysis, alcoholic aetiology (OR 1.76 [95% CI, 1.39–2.24]; $p < 0.001$) and smoking aetiology (OR 1.77 [95% CI, 1.39–2.26], $p < 0.001$) were positively associated with the presence of calcifications, while an autoimmune aetiology was negatively associated with calcifications (OR 0.15 [95% CI, 0.08–0.27], $p < 0.001$). Patients with pancreatic calcifications were more likely to have undergone pancreatic duct stenting (OR 1.59 [95%CI, 1.16–2.19], $p = 0.004$).

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https://doi.org/10.1016/j.pan.2019.08.009

Conclusion: The presence of pancreatic calcifications is associated with diverse aetiological risk factors in patients with CP. This observation attest to the understanding of CP as a complex disease and may have implications for disease classification.

The presence of pancreatic calcifications is a common finding in patients with chronic pancreatitis (CP) and has been included in most past and current systems for disease classification [1–6]. The finding of pancreatic calcifications on cross-sectional imaging thus provides a useful radiological biomarker that in a relevant clinical context can be used to establish a diagnosis of CP [7]. Notwithstanding the clinical usefulness of pancreatic calcifications in the context of CP diagnosis, the underlying pathophysiological process is still uncertain and it remains unclear why some patients develop calcifications while others do not [8–11]. An improved understanding of the parameters associated with calcifications may advance the understanding of CP and lead to better and more accurate systems for disease classification.

Patients with CP present with a wide spectrum of symptoms and disease complications. These include upper abdominal pain, exocrine and endocrine pancreatic insufficiency, as well as a number of less common complications such as common bile duct and duodenal stenosis [12]. In addition, many patients have a past history of recurrent acute pancreatitis and often multiple aetiological risk (genetic and environmental) can be identified in individual patients [13–15]. Taken together, these parameters may all be associated with the presence of pancreatic calcifications, but the relationships are not straight forward and past studies for 'risk factors' of calcifications have mostly been focused on single parameters or limited by small sample sizes [2,9–11,16–21]. In complex diseases, such as CP, where many parameters interact in complicated patterns, analysis of each variable independently often provides an incomplete picture of the overall disease state and may lead to bias [12,22,23]. Large-scale studies with adequate power for multivariate statistical modelling can be used to overcome this problem and provides a means to study interrelationship between disease parameters in a more comprehensive way [12,24].

In a multicentre cohort of more than 1500 patients with CP the aims of the study were: i) to determine the prevalence of pancreatic calcifications and ii) to determine associations between patient and disease characteristics and the presence of pancreatic calcifications using a multivariate statistical approach. In an additional analysis, we investigated iii) the associations between pancreatic calcifications and past or current endoscopic or surgical treatment.

Methods

This was a cross-sectional, multicentre study using data derived from the Scandinavian Baltic Pancreatic Club (SBPC) database. The SBPC database is an open multicentre prospective registration of patients with CP initiated in 2016 [23]. Data for the present study was derived from the database as of April 1st, 2019 and included data from 12 centres in eight countries in the Scandinavian-Baltic region and Russia (Moscow). The detailed study protocol and methodology of the SBPC database has been published previously [23]. We defined CP according to the M-ANNHEIM classification system and both patients with definitive and probable CP were included [5]. The study was approved by Institutional Review Boards at each participating centre.

Patient assessment parameters

Review of imaging studies (CT, MRCP, transabdominal and endoscopic US) was performed as part of routine clinical practice at the individual sites by radiologists, clinical pancreatologists or endoscopic ultrasonographers, and information on pancreatic calcifications was registered in the database. The imaging study obtained closest to the date of registration of the patient in the database was used. No distinction was made between ductal and peripheral located (side-branch) calcifications as this is often difficult to ascertain in a clinical scenario without additional second line imaging modalities such as MRCP or EUS [7]. Hence, the majority of patients only had one imaging modality registered at the time of study inclusion (most commonly a CT scan) and, as such, complementary imaging data sets were not available for most patients.

Information on patients' demographics (gender and age at diagnosis) and disease characteristics including aetiology and duration of CP, presence of diabetes as well as preceding history of recurrent acute pancreatitis were recorded based on review of medical records and patient interviews. The most likely aetiological risk factor(s) were designated by the treating physician according to the M-ANNHEIM system, which allow more than one aetiological risk factor to be ascribed to the individual patient. Risk-thresholds for alcohol consumption and smoking were not adopted in this process [5]. In the M-ANNHEIM system the term 'nicotine' is used to assign smoking as an aetiological risk factor, while the use of other nicotine sources (e.g. nicotine patches) were not considered as risk factors. Exocrine pancreatic function was characterized according to local practice at the individual sites using the faecal elastase concentration test, C13 mixed triglyceride breath test or faecal fat collection, and EPI was defined according to previously published criteria [25]. No stratification was made for EPI severity. Information on endoscopic treatment and pancreatic surgery was obtained from patient interviews and review of medical records. Endoscopic treatment included drainage procedures, common bile duct stenting and stenting of the pancreatic duct. Pancreatic surgery included drainage procedures, pancreatic resection or combined drainage and resection procedures. However, only a limited number of patients had undergone pancreatic surgery and consequently the data on surgical treatment was pooled for analysis.

Statistical analysis

Data are presented as numbers (%) for categorical data and as means (SD) for continuous data. Patient demographics and disease characteristics were compared for CP patients with and without calcifications using Student's *t*-test for continuous variables and Fisher's exact test for categorical variables (univariate analysis). Multivariable modeling was performed in agreement with the TRIPOD recommendations [26]. Logistic regression with backward selection was performed to assess the variables associated with the presence of calcifications in a multivariate model. Variables were included and removed one at a time according to their significance level ($p < 0.15$) until a final model was reached, but variables considered to have clinical relevance were forced back into the

model (EPI) [26]. Interaction between alcohol and smoking aetiology was determined using a nested log-likelihood test, comparing a model containing the variables as single terms with a model also including the interaction term [27]. The final logistic regression model included all the 1509 enrolled patients. Results from multivariate analyses were presented as odds ratios (ORs) with 95% confidence intervals (CI). A sensitivity analysis was performed by stratifying patients into one of four subgroups based on smoking and alcoholic aetiology (non-toxic, alcohol, smoking, alcohol and smoking) and differences in proportions of patients with and without calcifications were compared between aetiology subgroups using Fisher's exact tests. Finally, univariate logistic regression was used to analyse the odds of endoscopic or surgical treatment in patients with and without calcifications. Results from these analyses were also presented as ORs with 95% CI. A significance threshold of $p < 0.05$ was used. The software package STATA version 15.1 (StataCorp LP, College Station, Texas, USA) was used for statistical analyses.

Table 1
Patient, clinical and treatment characteristics of the study cohort (n = 1509).

Patient characteristics		
Sex, n (%)	Women	503 (33)
	Men	1006 (67)
Age at diagnosis, years ± SD		53.9 ± 14.5
Age distribution, n (%)	<30 years	95 (6)
	30–40 years	183 (12)
	40–50 years	310 (21)
	50–60 years	374 (25)
	60–70 years	325 (22)
	>70 years	222 (15)
Disease characteristics		
Duration of CP, years ± SD		4.3 ± 5.5
Duration of CP, n (%)	<5 years	1005 (67)
	5–10 years	324 (21)
	>10 years	180 (12)
Etiological risk factors, n (%)[a]	Alcohol	844 (56)
	Nicotine	895 (59)
	Nutritional	54 (4)
	Hereditary	115 (8)
	Efferent	133 (9)
	Immunological	111 (7)
	Miscellaneous	138 (9)
Recurrent acute pancreatitis, n (%)	Yes	625 (41)
	No	753 (50)
	Undetermined	131 (9)
Exocrine pancreatic insufficiency, n (%)		730 (48)
Diabetes mellitus, n (%)		568 (38)
Treatment		
Endoscopic therapy, n (%)	Drainage of pancreatic fluid collection	119 (8)
	Common bile duct stenting	187 (12)
	Pancreatic duct stenting	204 (13)
Surgery, n (%)	Pancreatic drainage procedure	45 (3)
	Pancreatic resection	59 (4)
	Combined drainage and resection	32 (2)

[a] Patients may have more than one etiological risk factor according to the M-ANNHEIM classification. Concomitant alcoholic and smoking aetiology were seen in 644 (43%) patients.

Results

On the date of data extraction, a total of 1756 patients with a diagnosis of CP were enrolled in the SBPC database. Among these, complete datasets regarding pancreatic calcifications and associated patient and disease characteristics were available for 1509 patients, which comprised the final study cohort. Patients had a mean age of 53.9 ± 14.5 years at the time of CP diagnosis and 1006 were men (67%). Detailed demographic and disease characteristics of the study cohort are reported in Table 1. According to the treating physician's designation, smoking was the most frequent etiological risk factor and present in 895 (59%) of patients, while alcohol misuse was considered an etiological risk factor in 844 (56%) of patients. In 644 patients (43%) smoking and alcohol misuse was considered coexisting risk factors.

Prevalence of pancreatic calcifications

Pancreatic calcifications were reported in 912 of the 1509 included patients corresponding to a calcification prevalence of 60.4% (95% CI, 57.9–62.9%).

Parameters associated with pancreatic calcifications

Patients with calcifying CP were more likely to be diagnosed with CP at an older age compared to patients without calcifications ($p < 0.001$) – Fig. 1a. Likewise, patients with long lasting CP were more likely to have pancreatic calcifications compared to patients

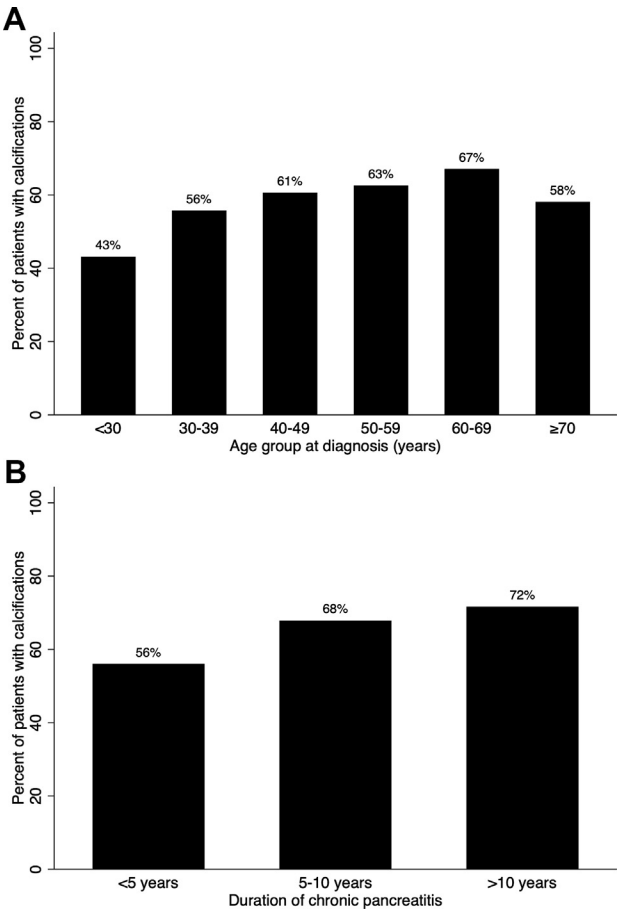

Fig. 1. Percentage of chronic pancreatitis patients with calcifications stratified by (A) age at diagnosis and (B) duration of chronic pancreatitis.

with short lasting disease ($p < 0.001$) – Fig. 1b. There were no differences in the proportion of patients with and without calcifications in relation to gender ($p = 0.12$) or past history of recurrent acute pancreatitis ($p = 0.40$) – Table 2. Patients with alcohol ($p < 0.001$) and smoking ($p < 0.001$) as aetiological risk factors were more likely to have pancreatic calcifications, while patients with an autoimmune aetiology were less likely to have calcifications ($p < 0.001$). There were no differences in the proportions of patients with and without calcifications in regard to the remaining aetiological risk factors. Finally, EPI ($p < 0.001$) and diabetes mellitus ($p < 0.001$) were more frequently observed in patients with calcifications – Table 2.

On multivariate analysis, age at diagnosis ($p < 0.001$), duration of CP ($p < 0.001$), alcoholic aetiology ($p < 0.001$) and smoking aetiology ($p < 0.001$) were significantly and independently associated with the presence of pancreatic calcifications. In contrast, patients with an autoimmune aetiology were less likely to have pancreatic calcifications ($p < 0.001$). We found no evidence of interaction between alcohol and smoking aetiology on the risk of calcifications ($p = 0.37$). As opposed to the results from univariate analysis, the presence of EPI ($p = 0.11$) and diabetes ($p = 0.11$) were not associated with pancreatic calcifications on multivariate analysis – Table 3 and Fig. 2.

Table 3
Multivariable analysis of patient and disease characteristics and the odds of having pancreatic calcifications.

		Odds ratio (95% CI)	P-value
Age at diagnosis		1.02 1.01–11.03)	<0.001
Duration of CP		1.05 (1.03–1.08)	<0.001
Aetiological risk factors	Alcohol	1.76 (1.39–2.24)	<0.001
	Nicotine	1.77 (1.39–2.26)	<0.001
	Immunological	0.15 (0.08–0.27)	<0.001
EPI		1.17 (0.93–1.48)	0.19
Diabetes mellitus		1.21 (0.95–1.55)	0.11

CP; chronic pancreatitis, EPI; exocrine pancreatic insufficiency.

Sensitivity analysis

Distributions of pancreatic calcifications according to alcoholic and smoking aetiology or their combination are illustrated in Fig. 3. Patients with alcoholic aetiology, smoking aetiology and combined alcoholic and smoking aetiology all had an increased risk of calcifications compared to patients with a non-toxic aetiology (all $p < 0.001$). Also, patients with combined alcoholic and smoking aetiology had an increased risk of calcifications compared to patients with either alcoholic aetiology (73% vs. 62%, $p = 0.003$) or smoking aetiology (73% vs. 64%; $p = 0.01$). The number of patients with calcifications was proportionate between patients with alcoholic or smoking aetiology (64% vs. 62%; $p = 0.68$).

Association between pancreatic calcifications and endoscopic or surgical procedures

Patients with calcifying CP were more likely to have undergone pancreatic duct stenting compared to patients with non-calcific CP (16 vs. 10%; $p = 0.004$). In contrast, there were no associations between calcifications and endoscopic drainage ($p = 0.14$), common

Table 2
Associations between patient and disease characteristics and the presence of pancreatic calcifications (univariate analysis).

		Pancreatic calcifications (n = 912)	No pancreatic calcifications (n = 597)	P-value
Sex, n (%)	Women	290 (32)	213 (36)	0.12
	Men	622 (68)	384 (64)	
Age at diagnosis, years ± SD		54.3 ± 13.8	52.1 ± 15.3	0.004
Age at diagnosis, n (%)	<30 years	41 (5)	54 (9)	0.001
	30–40 years	102 (11)	81 (14)	
	40–50 years	188 (21)	122 (20)	
	50–60 years	234 (26)	140 (23)	
	60–70 years	218 (24)	107 (18)	
	>70 years	129 (14)	93 (16)	
Duration of CP, years ± SD		4.8 ± 5.8	3.5 ± 5.0	<0.001
Duration of CP, n (%)	<5 years	563 (62)	442 (74)	<0.001
	5–10 years	220 (24)	104 (17)	
	>10 years	129 (14)	51 (9)	
Etiological risk factors, n (%)	Alcohol	594 (65)	250 (42)	<0.001
	Nicotine	631 (69)	264 (44)	<0.001
	Nutritional	31 (3)	23 (4)	0.64
	Hereditary	59 (6)	56 (9)	0.04
	Efferent	77 (8)	56 (9)	0.53
	Immunological	15 (2)	96 (16)	<0.001
	Miscellaneous	77 (8)	61 (10)	0.25
Recurrent acute pancreatitis, n (%)[a]		380 (46)	245 (44)	0.40
EPI, n (%)		483 (53)	247 (41)	<0.001
Diabetes mellitus, n (%)		376 (41)	192 (32)	<0.001

[a] A history of recurring acute pancreatitis was undetermined in 131 patients and these were not included in the analysis. CP; chronic pancreatitis. EPI; exocrine pancreatic insufficiency.

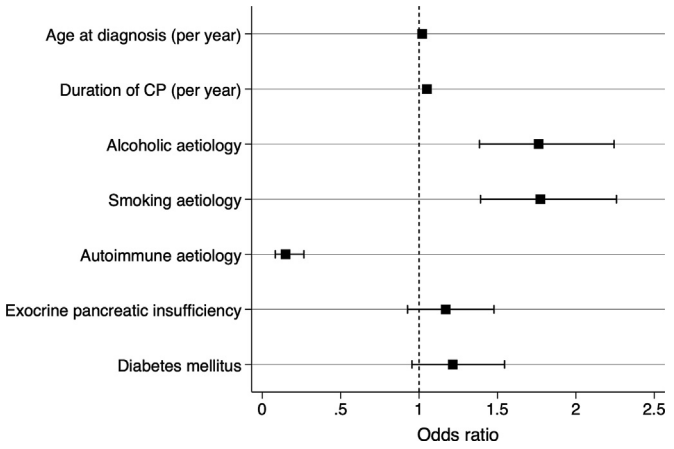

Fig. 2. Forest plot of the multivariable logistic regression model for the presence of calcifications vs. no calcifications in patients with chronic pancreatitis. Whiskers represent 95% confidence intervals.

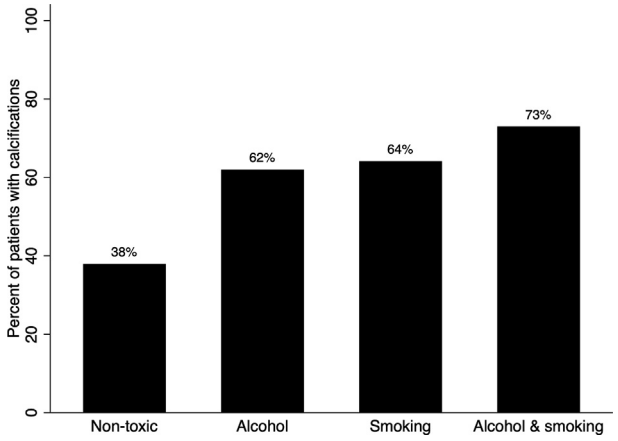

Fig. 3. Percentage of chronic pancreatitis patients with calcifications stratified by smoking and alcoholic disease aetiology (sensitivity analysis).

bile duct stenting ($p = 0.48$) or pancreatic surgery ($p = 0.46$) – Table 4.

Discussion

We investigated the prevalence of pancreatic calcifications and associated patient and disease characteristics in a multi-centre cohort of more than 1500 patients with CP. Sixty percent of patients had pancreatic calcifications, but the prevalence of calcifications was highly dependent on disease aetiology with an increased risk of calcifications in patients with smoking and alcoholic aetiology, while an autoimmune aetiology of CP was negatively associated with the presence of calcifications. In contrast to most previous studies, the presence of pancreatic calcifications was not associated with exocrine or endocrine pancreatic insufficiency after adjustment for disease duration and patients' age at diagnosis. Taken together these findings underline the heterogenous presentation of CP and may have implications for the classification of this entity.

Prevalence of pancreatic calcifications

Approximately 60% of the patients enrolled in the SBPC cohort had pancreatic calcifications. This estimate is comparable to those observed in other multicentre studies from North America (55%) [28] and Italy (62%) [29], while the prevalence of calcifications in a Spanish multicentre cohort was somewhat lower (35%), possible reflecting different CP populations or differences in diagnostic approaches [30]. There are limited population based morphological data available for CP but in a population-based evaluation from Olmsted County the prevalence of calcifications was 69% [31]. This is slightly higher compared to that observed in specialized centres, which may be explained by a higher proportion of patients with non-toxic aetiologies in specialized settings. Taken together, these data underline that the presence of pancreatic calcifications is a frequent finding in patients with CP and typically seen in more than half of patients in Western populations.

Risk factors for pancreatic calcifications

Different aetiologies of CP were associated with different risks of pancreatic calcifications. For example, 'classical CP' typically seen in subjects with a history of smoking and alcohol misuse was frequently characterized by calcifications, while patients with autoimmune aetiology of CP rarely had pancreatic calcifications. These findings are in line with past studies where excessive alcohol consumption and smoking have also been associated with an increased risk of calcifications [2,8,32]. As an extension of past studies, we demonstrated that the effects of alcohol and smoking were independent, and that the presence of both risk factors conveyed an increased risk of calcifications as compared to patients with either smoking or alcoholic aetiology. The underlying pathophysiological processes are not fully understood and probably involve a number of mechanisms. For example, the pancreatic juice is supersaturated in calcium and bicarbonate ions and a mechanism controlling calcium-carbonate stone formation is therefore necessary to prevent stone formation [33]. One such mechanism has been shown to involve the presence of the glycoproteins lithostatine and glycoprotein-2 that both are released from the apical surface of the acinar cells [34,35]. The presence of these

Table 4
Probability of endoscopic or surgical treatment in patients with and without pancreatic calcifications.

	Pancreatic calcifications (n = 912)	No pancreatic calcifications (n = 597)	Odds ratio (95% CI)	P-value
Endoscopic drainage of pancreatic fluid collection	81 (9)	38 (6)	1.43 (0.96–2.14)	0.08
Common bile duct stenting	108 (12)	79 (13)	0.88 (0.65–1.20)	0.42
Pancreatic duct stenting	142 (16)	62 (10)	1.59 (1.16–2.19)	0.004
Any pancreatic surgery[a]	74 (8)	53 (9)	0.91 (0.63–1.31)	0.60

Data are presented as numbers (%).
[a] Due to low number of patients undergoing pancreatic surgery (drainage, resection or combined drainage and resection) the different surgical procedures were pooled for analysis.

glycoproteins in the pancreatic juice delays crystal formation and inhibit growth of preformed calcium-carbonate crystals, but the lithostatic effect may be disturbed by alcohol misuse and smoking [33]. The importance of smoking in this context is further illustrated by prospective studies showing that smoking accelerates the formation of pancreatic calcifications and that smoking cessation in the first years from the clinical onset of CP reduces the risk of developing pancreatic calcifications [8,10,18].

The negative association between autoimmune aetiology of CP and the odds of having pancreatic calcifications is in line with recent observations from a Japanese multi-centre study. Hence, in the Japanese study only 31 (5%) out of 621 patients with type 1 autoimmune pancreatitis had calcifications and as such, the presence of pancreatic calcifications is not a common finding in this context.

The odds for calcifications increased with prolonged disease duration which is in keeping with observations from past studies of patients with alcoholic and 'idiopathic' CP [2,21]. However, more than 50% of the patients with short disease duration (<5 years) in our cohort had calcifications, which implies that calcifications can develop during all stages of CP and is not a phenomenon restricted to advanced or end stage disease. This notion was further supported by the dissociation between calcifications and pancreatic exocrine or endocrine insufficiency observed on multivariate analysis. Thus the historical conception of pancreatic calcifications as an end-stage defining feature of CP that evolve in conjunction with development of functional impairment is not supported by our data [1]. Interestingly, recent observations imply that pancreatic calcifications may even spontaneously dissolve over time, although this is probably a rare event [36].

The patient's age at diagnosis was independently associated with calcification risk and patients presenting at an older age category were more likely to have calcifications compared to their younger counterparts. This is in line with previous observations of patients with idiopathic CP, where 'late idiopathic CP' was typically characterized by a painless form of CP with massive pancreatic calcifications and exocrine pancreatic insufficiency, while patients with 'early onset idiopathic CP' typically had severe pain and less frequently calcifications and functional impairment [2,32].

Finally, the presence of pancreatic calcifications was associated with an increased risk of pancreatic duct stenting. This is an expected finding and reflects common clinical practice and recommendations from current guidelines where an obstructed main pancreatic duct (due to stricture or stone) is regarded an indication for endoscopic therapy in patients with relevant symptoms [37,38].

Implications for classification of chronic pancreatitis

The findings of the present study underline that the morphological presentation of CP (calcific vs. non-calcific disease) is variable and dependent on the underlying disease aetiology. This has implications for the understanding and classification of CP. Hence, the term 'CP' is currently used to characterize a number of different chronic inflammatory disorders of the pancreas including 'classic calcifying CP', autoimmune pancreatitis, hereditary pancreatitis as well as early and late idiopathic CP. These entities are all characterized by diverse morphological features, including different calcification frequencies, as well as distinct clinical presentations and management strategies. Given this heterogeneity it has been proposed that the term 'CP' is probably used too general at present [39]. This may blur comparisons across studies and lead to misconceptions. Inspired by the terminology used to embrace the spectrum of inflammatory bowel disorders, the term 'chronic inflammatory diseases of the pancreas' has been suggested as a more appropriate term to describe the different types of chronic inflammatory disorders currently labelled 'CP', thus reserving 'CP' to characterize the typical patient with calcifying CP resulting from alcohol or smoking misuse [39].

Study limitations

Our study has some limitations that need to be mentioned. First, the cross-sectional nature precludes any causal inference between the observed associations. However, most findings are supported by previous longitudinal studies and/or conceivable mechanistic linkage from basic studies. Second, no distinction between calcifications located in the main pancreatic duct (and thus amendable to endoscopic treatment) and peripheral located (side-branch) calcifications were made. However, the exact localization of calcifications is often difficult to ascertain in a clinical scenario without additional second line imaging modalities such as MRCP or EUS, which was not available for this large cohort of patients [7]. Third, only a past history of recurring pancreatitis was considered as a risk factor for calcifications, while the effect of a single episode of acute pancreatitis was not explored. We choose this approach as a single episode of acute pancreatitis only confers a limited risk of subsequent development of chronic pancreatitis (approximately 10%), while the presence of recurring acute pancreatitis significantly increases this risk (approximately 36%) [40]. Also, it would not be possible to include single as well as recurring acute pancreatitis in the same multivariate model as these variables would invariably be closely correlated and thus introduce collinearity in the regression model. Fourth, we did not collect data on the number of acute pancreatitis attacks in patients with recurring acute pancreatitis. This may explain the lack of association between pancreatic calcifications and a past history of recurring pancreatitis. Hence, it is plausible that patients with a large number of acute pancreatitis episodes have a different risk for calcifications than patients with a limited number of episodes. Finally, our findings are restricted to an adult Western population dominated by alcohol and smoking related CP and thus need further elaboration in paediatric populations and in populations with different aetiological risk factor profiles [41,42].

Conclusion

The presence of pancreatic calcifications is associated with diverse aetiological risk factors in patients with CP. This finding attests to the understanding of CP as a complex disease and may have implications for the classification of this entity.

Acknowledgements

All authors declare no conflicts of interest. Funding source: None.

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