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Prevalence of chronic pancreatitis: Results of a primary care physician-based population study

Gabriele Capurso[a,*], Livia Archibugi[a], Piera Pasquali[d], Alessandro Aceti[c], Paolo Balducci[c], Patrizia Bianchi[b], Francesco Buono[b], Stefano Camerucci[c], Rosanna Cantarini[c], Sergio Centofanti[d], Patrizia Colantonio[c], Riccarda Cremaschi[b], Sergio Crescenzi[b], Caterina Di Mauro[c], Davide Di Renzi[c], Andrea Filabozzi[d], Alfonso Fiorillo[c], Giuseppe Giancaspro[c], Paola Giovannetti[c], Giuseppe Lanna[e], Claudio Medori[c], Emilio Merletti[e], Enzo Nunnari[d], Francesca Paris[e], Marco Pavone[d], Angela Piacenti[d], Almerindo Rossi[d], Maria Cristina Scamuffa[c], Giovanni Spinelli[b], Marco Taborchi[e], Biagio Valente[c], Antonella Villanova[d], Alberto Chiriatti[d], Gianfranco Delle Fave[a]

[a] *Digestive and Liver Disease Unit, S. Andrea Hospital, University Sapienza, Rome, Italy*
[b] *Azienda Sanitaria Locale Roma 1, Italy*
[c] *Azienda Sanitaria Locale Roma 2, Italy*
[d] *Azienda Sanitaria Locale Roma 3, Italy*
[e] *Azienda Sanitaria Locale Roma 5, Italy*

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ABSTRACT

Background: Data on chronic pancreatitis prevalence are scanty and usually limited to hospital-based studies.
Aim: Investigating chronic pancreatitis prevalence in primary care.
Methods: Participating primary care physicians reported the prevalence of chronic pancreatitis among their registered patients, environmental factors and disease characteristics. The data were centrally reviewed and chronic pancreatitis cases defined according to M-ANNHEIM criteria for diagnosis and severity and TIGAR-O classification for etiology.
Results: Twenty-three primary care physicians participated in the study. According to their judgment, 51 of 36.401 patients had chronic pancreatitis. After reviewing each patient data, 11 turned out to have definite, 5 probable, 19 borderline and 16 uncertain disease. Prevalence was 30.2/100.000 for definite cases and 44.0/100.000 for definite plus probable cases. Of the 16 patients with definite/probable diagnosis, 8 were male, with mean age of 55.6 (±16.7). Four patients had alcoholic etiology, 5 post-acute/recurrent pancreatitis, 6 were deemed to be idiopathic. Four had pancreatic exocrine insufficiency, 10 were receiving pancreatic enzymes, and six had pain. Most patients had initial stage and non-severe disease.
Conclusions: This is the first study investigating the prevalence of chronic pancreatitis in primary care. Results suggest that the prevalence in this context is higher than in hospital-based studies, with specific features, possibly representing an earlier disease stage.

1. Introduction

Chronic pancreatitis (CP) is a serious progressive disease, recently defined as a pathologic fibro-inflammatory syndrome that develops in individuals with genetic, environmental and/or other risk factors [1]. Epidemiological data on CP are scanty [2] and its incidence varies from 4 to 13/100.000 [2–4], with a progressive increase of the rate over time [5]. Although life expectancy of CP patients is shorter than that of healthy individuals [6], CP is usu-

* Corresponding author at: Digestive and Liver Disease Unit, S. Andrea Hospital, University Sapienza, Rome, Via di Grottarossa 1035, 00189, Rome, Italy. Fax: +39 0633775526.
E-mail address: gabriele.capurso@gmail.com (G. Capurso).

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ally a long-standing disease and the above indicated incidence is hardly reflected by the low prevalence of CP in most studies, with rates ranging from 3 to 41/100.000 [2,5]. A formal diagnosis of CP is often difficult to be made and most of those studies are hospital-based and therefore might not represent the general population. Therefore, most likely, epidemiological studies tend to underestimate the prevalence of CP. Indeed, the autoptic prevalence of CP is much higher, ranging from 2% in controls to about 20% in patients with alcohol-related liver disease [7,8]. Interestingly, the only population-based study conducted so far on the epidemiology of CP yielded the highest prevalence of 41/100.000 [3].

There are no studies aimed at investigating the prevalence of CP in the primary care setting. However, as patients with CP present with common symptoms such as pain, weight loss and diabetes, and usually require diagnostic tests and drugs' prescription, they are likely to be followed by their primary care physicians (PCPs). The Italian National Health Service is administered on a regional basis by local health authorities (Azienda di Sanità Locale/ASL), with all citizens having a dedicated PCP who keeps track of their chronic disorders, investigations and treatments through electronic databases. According to recent studies, data on disease prevalence and outcomes obtained by healthcare administrative data collected by Local Health Authorities in five Italian regions were very similar to the estimates from clinical data collected by PCPs, suggesting the genuineness of data obtained through this approach [9].

We hypothesized that Italian PCPs might be in an ideal position to investigate the actual prevalence of CP. This is because they see not only patients with advanced disease that need frequent drug prescription for the management of pain, and exocrine or endocrine pancreatic insufficiency, but also patients in the early phases of CP who might not be seen by gastroenterologists or surgeons.

We therefore aimed at investigating the prevalence of chronic pancreatitis in the primary care setting.

2. Methods

2.1. Study protocol

One-hundred and fifty-four primary care physicians (PCPs) of the Rome area were invited to take part in three educational meetings on CP and treatment of pancreatic exocrine insufficiency (PEI) organized at S. Andrea Hospital between March 2014 and March 2015. All of them participated in at least one of the meetings. During each meeting, they were invited to participate in the present study and, after the last meeting, those who agreed were contacted by email to do so. In case of no reply, or incomplete feedback a second or third email reminder was sent. In case of no reply to any of those messages, the PCP was considered a non-participant. Each participating PCP was asked to report the area of Rome in which they worked and the total number of patients registered at their practice. Furthermore, PCPs interrogated their electronic database, prescription reports and other available registries and reported the number of patients affected by CP, filling in a specific form with details about environmental factors and disease characteristics of each patient with CP during a face to face interview whenever possible (see Supplementary material). The study lasted 9 months, between March 2015 and December 2015. The study investigation form included patients' sex and age, age at diagnosis of CP and etiology of CP. Data on morphological abnormalities and imaging procedures performed were also recorded. The presence of pain, exocrine insufficiency and diabetes, and the need of medical treatment with pancreatic enzyme replacement therapy (PERT) were also recorded. PCPs were invited to refer patients to the pancreatic disorders clinic at S. Andrea Hospital for further evaluation if needed, or in case of "uncertain" diagnosis of CP. The local IRB approved the study and the enrolled patients gave informed consent.

2.2. Investigated factors and classification

The forms were reviewed by a physician (L.A.) with expertise in pancreatic disorders that, accordingly, classified CP cases. The diagnosis of CP was defined according to the M-ANNHEIM diagnostic criteria of chronic pancreatitis [10], as definite CP, probable CP or borderline CP. Etiology of CP was evaluated according to the TIGAR-O classification [11], with data on exposure to toxic agents such as alcohol and smoking, suspect of genetic or autoimmune form, previous episodes of acute pancreatitis, and obstructive causes recorded. The stages of the disease were classified according to the M-ANNHEIM clinical staging of CP classification [10] in 5 stages: 0 stage of subclinical (asymptomatic) CP, 1 stage of symptomatic CP without pancreatic insufficiency, 2 stage of partial pancreatic insufficiency, 3 stage of painful complete pancreatic insufficiency, 4 stage of secondary painless CP. The severity of the disease was classified according to the M-ANNHEIM severity index of chronic pancreatitis [10] as minor, increased, advanced, marked, exacerbated. The presence of pain, exocrine or endocrine pancreatic insufficiency and osteoporosis were also recorded, as well as the use of PERT. Regarding the morphological abnormalities that were used to define diagnosis and severity of disease, the last investigation of whom the PCP was aware was considered.

2.3. Statistical analysis

Results are reported as absolute number and percentages for categorical variables and for continuous variables as mean and standard deviation. We performed a *post hoc* power calculation, in order to verify if the evaluated sample population was sufficient to avoid an underestimation of prevalence. The sample size (n) is a function of the expected prevalence and precision for a given level of confidence expressed by the z statistic and is therefore directly proportional to the prevalence of the disease (P) and inversely proportional to the allowable error (d) which is a surrogate of precision. The formula used is: $n = (z2)\, P\, (1 - P)/d2$ [12]. As there are no available data on the prevalence of chronic pancreatitis in Italy in the primary care setting we hypothesized that it might have been similar to that reported by Yadav et al. (41.7/100.000) in a "population-based" study. Therefore, with an allowable error equal to P/2 as typically suggested for rare diseases, and a z value of 1,96 (that corresponds to a 95% confidence with normal distribution), the obtained needed sample size n = 36,781.

3. Results

3.1. Primary care physicians participation rate

Out of the 154 PCPs, 144 (93.5%) initially agreed to be contacted. However, 121 (84%) of them eventually did not reply to the repeated invitations and were considered non-participants. Twenty-three (16%) replied and sent data on both the number of total patients registered at their practice and the prevalent cases of CP among them. There were no differences between the 23 PCPs that participated in the study and the 121 that did not, regarding sex (male 60.0% vs 62.1%; p = 1.00) and age (mean 53.4 ± 12.3 vs 55.1 ± 13.1; p = 0.56). There are six health assistance districts in the metropolitan area of Rome (ASL: RM1, RM2, RM3, RM4, RM5, RM6) covering a total population of about 4.290.000 inhabitants. The 23 participating PCPs were distributed among the four largest districts (5 PCPs in RM1, 7 PCPs in RM2, 6 PCPs in RM3, 5 PCPs in RM5) covering 3.511.000 inhabitants without apparent bias.

Table 1
Features of the 16 patients with a definite or probable CP diagnosis.

Patient	Gender	Age at diagnosis	Etiology (TIGAR-O)	Smoking	Alcohol	PEI	PERT	Diabetes (type and therapy)	Duration of follow-up (years)	Morphology at last examination performed	Diagnosis
1	M	45	Idiopathic	No	No	Yes	Yes	No	12	Wirsung dilation	Definite
2	F	33	Post biliary RAP	No	No	No	Yes	No	5	Wirsung dilation	Definite
3	F	50	Post alcoholic AP	Yes	Yes	No	Yes	No	9	Wirsung dilation	Definite
4	M	64	Idiopathic	No	No	Yes	Yes	No	1	Wirsung dilation, parenchymal heterogeneity, pancreatic atrophy	Definite
5	M	38	Post alcoholic AP	Yes	Yes	Yes	Yes	Yes (type 3c – insulin)	8	Wirsung dilation, calcifications, pancreatic atrophy	Definite
6	F	63	Toxic	Yes	Yes	No	No	No	1	Irregular Wirsung, parenchymal heterogeneity	Probable
7	F	76	Idiopathic	No	No	No	No	Yes (type 3c – insulin)	3	Wirsung dilation	Definite
8	F	49	Post biliary AP	No	No	No	No	No	4	Wirsung stenosis and dilation	Definite
9	F	77	Obstructive (ampullary lesion)	No	No	No	No	No	2	Wirsung dilation, parenchymal heterogeneity	Probable
10	F	50	Post AP	No	No	No	Yes	No	17	Persistent pseudocyst, parenchymal heterogeneity	Probable
11	M	60	Toxic	Yes	Yes	Yes	Yes	No	1	Wirsung dilation, parenchymal heterogeneity	Definite
12	M	33	Idiopathic	No	No	No	No	Yes (type 3c – insulin)	4	Pancreatic calcifications	Definite
13	M	90	Idiopathic	No	Yes	No	Yes	No	1	Pancreatic calcifications	Definite
14	M	60	Toxic	Yes	No	Yes	Yes	No	1	Wirsung dilation, parenchymal heterogeneity	Definite
15	F	37	Idiopathic	No	No	No	Yes	No	18	Persistent pseudocyst, parenchymal heterogeneity	Probable
16	M	65	Toxic	No	Yes	No	No	Yes (type 2 – metformin)	8	Visible side branches, parenchymal heterogeneity	Probable

M = male.
TIGAR-O = toxic-metabolic; idiopathic; genetic; autoimmune; recurrent and severe acute pancreatitis; obstructive.
RAP = recurrent acute pancreatitis.
AP = acute pancreatitis.
PEI = pancreatic exocrine insufficiency.
PERT = pancreatic exocrine replacement therapy.

Table 2
Clinical staging and severity of CP in the 16 patients with a definite or probable diagnosis.

	Number (%)
Clinical staging	
Subclinical (asymptomatic)	4 (25%)
Symptomatic without pancreatic insufficiency	2 (12.5%)
Partial pancreatic insufficiency	8 (50%)
Painful complete pancreatic insufficiency	0 (0%)
Secondary painless	2 (12.5%)
Severity	
Minor	12 (75%)
Increased	4 (25%)
Advanced	0 (0%)
Marked	0 (0%)
Exacerbated	0 (0%)
Clinical features	
Exocrine insufficiency alone	3 (18.7%)
Endocrine insufficiency alone	3 (18.7%)
Combined exocrine and endocrine insufficiency	1 (6.2%)
Pain	6 (37.5%)
PERT	10 (62.5%)

PERT = pancreatic enzyme replacement therapy.

3.2. Prevalence of chronic pancreatitis

The total number of patients registered at the 23 participating PCPs practice was 36.401, with a mean of 1.400 (±226) registered patients per PCP. The number of reported forms with data on prevalent cases of PC was 51. The mean number of cases reported from each PCP ranged from 0 to 3 (mean 2.2 ± 1.8). These forms were reviewed, and the cases were accordingly classified as: definite CP (n = 11), probable CP (n = 5), borderline CP (n = 19) and uncertain CP (n = 16). Of these 51 patients, 18 (35.3%) were seen at S. Andrea Hospital Pancreatic Disorders outpatient clinic for further evaluation. The prevalence of CP was calculated taking into account only definite and probable cases and was of 16 CP cases/36.401 patients, equal to 44.0/100.000. If only definite cases were considered, the prevalence was 30.2/100.000.

3.3. General features and etiology of CP

Of the 16 patients with a definite or probable CP diagnosis, 8 were male with a mean age at diagnosis being 55.6 (±16.7). As far as etiology, according to the TIGAR-O classification [11], 4 patients were diagnosed with alcoholic etiology, 5 with post-acute/recurrent acute pancreatitis, 1 with obstructive etiology and 6 with idiopathic CP (see Table 1). There were no cases of autoimmune pancreatitis. Overall, 4 of the 16 patients were smokers (2 with alcoholic, 1 with post-acute and 1 with idiopathic etiology).

3.4. Clinical staging and severity of CP

According to the M-ANNHEIM clinical staging of CP classification [10], 4 (25%) patients were of stage 0 of subclinical (asymptomatic) CP, 2 (12.5%) of stage 1 of symptomatic CP without pancreatic insufficiency, 8 (50%) of stage 2 of partial pancreatic insufficiency, 0 of stage 3 of painful complete pancreatic insufficiency, 2 (12.5%) of stage 4 of secondary painless CP. The severity of the disease was classified according to the M-ANNHEIM severity index of chronic pancreatitis [10], and 12 (75%) patients were classified as with minor, 4 (25%) with increased, 0 with advanced, 0 with marked, and 0 with exacerbated disease (Table 2).

3.5. Symptoms and treatment of CP

Four (25%) of the 16 patients had diagnosis of pancreatic exocrine insufficiency (diagnosed in 2 cases by frank steatorrhea and in other 2 by low fecal elastase levels). However, 10 patients were receiving treatment with PERT (62.5%). Overall, fecal elastase was measured in only 4 cases. The mean dose of PERT was 50.000 lipase units per day (±37.000). Four patients had endocrine insufficiency (25%). Six (37.5%) were reported to have pain due to chronic pancreatitis.

4. Discussion

This is one of the few studies investigating the prevalence of CP, and the first specifically conducted in the setting of primary care assistance. The present results suggest that the prevalence of CP in this context is of at least 30.2/100.000. This figure only considers definite cases according to the M-ANNHEIM classification, and increases up to 44.0/100.000 considering also probable cases. Mean age at diagnosis of CP cases was 56 years, half of the patients were female, and most of them had mild disease, with an alcoholic etiology in only 25% of cases.

Previous studies investigating the prevalence of CP showed heterogeneous results. The prevalence of CP ranged, indeed, from 3 to 41/100.000 [2–4,13,14]. Most of the published studies, however, were hospital-based and might have therefore underestimated the prevalence of the disease evaluating only symptomatic cases. Interestingly, in terms of prevalence, the present results are more similar to those obtained by Yadav et al. [3] in a study conducted in Olmsted County where most individuals are seen at a single Institution, therefore reflecting a "population-based" prevalence.

As far as regards the characteristics of the patients, the mean age of 55 years at diagnosis is similar to that of 58 years previously reported by Yadav et al. [3]. In the present study, however, there was a slightly higher rate of female patients and a lower rate of alcoholic etiology (25%) as compared with previous studies, with a high prevalence of "post-acute pancreatitis" or idiopathic forms. A shift towards a higher rate of non-alcoholic etiology of CP and an increase of female patients, however, has already been reported by others [15]. In two large multicenter studies conducted in the US [16] and Italy [17], 44% of CP cases had an alcoholic etiology, but this rate was much lower in female patients. Notably, both these studies were collecting data of patients seen mainly at referral Centers for pancreatic disorders that might be subject to a spectrum bias and not include mild cases, while patients seen in primary care might have distinct etiology with lower rate of alcohol abuse and more frequent post-acute forms. In keeping with this hypothesis are the findings of a study evaluating pancreatitis cases seen by PCPs in the UK, that reported alcohol abuse in only 20% of CP cases [18]. In the present study the etiology was initially attributed by the PCP that took care of the patient, and these data were centrally reviewed. We did not choose to define an exact cut-off of alcohol intake for this definition. Indeed, although the Zürich conference on alcoholic chronic pancreatitis [19] agreed to define alcoholic chronic pancreatitis as chronic pancreatitis that occurs following a daily intake of alcohol equal to or greater than 80 g per day for several years in men and less in women, the intake of smaller amounts of alcohol may also result in pancreatic damage [20].

The transition from acute to chronic pancreatitis is a described phenomenon [21] and accounts for about 10% of acute pancreatitis cases [22,23]. Notably, the most recent attempt of defining CP describes it as a "syndrome" diagnosed in "individuals who develop persistent pathogenic responses to parenchymal injury or stress" and stressed the model of disease development including transition from severe or recurrent acute pancreatitis to early CP and eventually established CP [1]. At any rate, as in the present study the etiology was defined based on the treating primary care physician's diagnosis and only 35% of cases were also seen at a tertiary care Center clinic, a possible quota of misdiagnosis cannot be excluded. Our findings of mild disease in most cases also suggest that PCPs might observe some CP patients with very "early" phases of disease who might not be seen by gastroenterologists or surgeons. This hypothesis has been previously proposed by Levy et al. when discussing the reasons for the apparent discrepancy between the rates of incidence and prevalence of CP in most published studies [2]. In this view, it is possible that more severe cases admitted to hospital and diagnosed due to acute bouts who died, or are not seen by their PCP due to a very poor compliance related to alcohol addiction, have been missed in our analysis.

A quarter of the 16 patients with definite or probable CP observed in the present study were diagnosed by their PCPs with pancreatic exocrine insufficiency, although fecal elastase evaluation was only rarely requested. Interestingly, however, pancreatic enzyme replacement therapy (PERT) was prescribed in 10 patients (62.5%). The daily dosage of PERT (mean 50.000 lipase units), however, seems low compared to that suggested by the Italian guidelines [24]. These results suggest that PCPs might not be completely aware of the indication and optimal dosing of PERT in CP patients. Indeed, PERT was also prescribed in patients without defined PEI but who reported pain (6 of 16, 37.5%), while there is no evidence for this indication [25]. Interestingly, Sikkens et al. also reported that many patients with pancreatic exocrine insufficiency caused by chronic pancreatitis are under-treated in the Netherlands [26].

Our study has some strengths. It is the first attempt to evaluate the prevalence of chronic pancreatitis in the setting of primary care with results that seem reliable and in line with the few population-based data on CP. We performed a *post hoc* power calculation that suggested that the target population of about 36.000 patients that was obtained from the participating PCPs was adequate. Validated scores were employed to classify the etiology and the severity of each case. The present results represent a picture of the real life care of patients with CP not evaluated in tertiary care Centers, and suggest the need for a collaboration between PCPs and hospitals for the cure of CP patients. The low participation rate of the invited PCPs is a limitation, but it was not unexepected and is similar to that obtained in other studies with a similar design [27]. However, there were no apparent differences among participants and non-participants, and a low participation rate is frequent in this kind of study [4,28]. Finally, as the data of the present study are mainly based on the clinical evaluation and judgment of PCPs who are not experienced in pancreatic disorders, misclassification might have occurred in some instances. We tried and limit this kind of bias in several ways. First, all PCPs initially took part in educational meetings on chronic pancreatitis and the treatment of pancreatic exocrine insufficiency (PEI) held at our University hospital. Secondly, all forms containing recorded data on CP cases were reviewed by a physician with expertise in pancreatic disorders who classified the patients in terms of staging and severity of disease. Finally, the opportunity of a visit at the Pancreatic Disorders outpatient clinic for further evaluation was offered for all cases, and a third of the patients with potential CP diagnosis were accordingly seen there.

In conclusion, the prevalence of chronic pancreatitis in the primary care setting is higher than in previous hospital-based studies, with a high rate of female patients, mild disease, and non-alcoholic etiology. These results highlight the importance of the collaboration between PCPs and tertiary Centers for the evaluation of patients with pancreatic disorders and the need of more population-based

studies to better investigate the actual epidemiology and the natural history of chronic pancreatitis.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2016.12.024.

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