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Prevalence and correlates of Benign Pancreatic Hyperenzymemia in a large general population sample: The Damocles sword perception

Pierpaolo Cavallo [a, f, *], Luna Carpinelli [b], Fabiana Zingone [c], Immacolata Sepe [d], Mario De Santis [e], Carolina Ciacci [b]

[a] Department of Physics, University of Salerno, Salerno, Italy
[b] Department of Medicine, Surgery, Dentistry, Scuola Medica Salernitana, University of Salerno, Salerno, Italy
[c] Department of Surgery, Oncology, and Gastroenterology, University of Padua, Padua, Italy
[d] Diagnostica Cavallo, Centro Ricerca Albo Laboratori MIUR DM 593/2000, Salerno, Italy
[e] Mega Ellas, Consorzio Cooperative MMG, Salerno, Italy
[f] ISC-CNR, Istituto Sistemi Complessi del CNR, Rome, Italy

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ABSTRACT

Background: Benign Pancreatic Hyperenzymemia (BPH) is characterized by a long-term increase of serum pancreatic enzymes (PE) in otherwise healthy subjects. The study investigates the prevalence and correlates of the condition using data from Electronic Health Records (EHR) in a large sample of general population, to identify subjects potentially affected by BPH.
Methods: Cross-sectional retrospective observational study integrated by a follow-up visit.
Results: The database of a reference laboratory identified, out of 577.251 admittances from 2011 to 2015, 4964 patients tested at least for one PE assay and 1688 subjects who had at least 3 PE tests (normal or increased) over two years. Forty-two individuals showed an increase of PE at least three times throughout 2 years without any evidence of pancreatic disease, even after matching with the ICD 9-CM code in the GPs database. Data retrieved at follow-up visit showed that for 34 the diagnosis of BPH could be made.
Conclusions: Our data indicate that BPH prevalence among subjects underwent blood testing for multiple PE testing is 2%. This condition, even if not a disease, is perceived by nearly all the BPH patients as a serious threat to their life. Further studies are needed to manage its heavy psychological impact.

Introduction

Digestive enzymes digest polymeric macromolecules to facilitate their absorption by the body. Among the digestive enzymes, amylase and lipase are particularly relevant for human physiopathology. The pancreas mainly produces the amylases (P-amylases), followed by the salivary glands (S-amylases). Two genes *AMY1* and *AMY2*, located on the chromosome *1p2113*, synthesized the two proteins [1]. A minimal quantity of amylases, similar to s-amylases, can also be found in the biliary ductules and ducts and is synthesized by the gene *AMY2B*. However, the *AMY2B* gene is also expressed in the lung [2]. The α-amylases (1-4-α glucan glucanhydrolases; EC 3.2.1.1) are monomeric Ca-binding proteins of about 50.000 Da that cleave the polysaccharide α-1-4 glycoside bonds [3].

The lipases (tryacilglicer-acil-hydrolases, EC 3.1.1.3) are proteins of about 40.000 Da that at a basic pH hydrolyze the ester bond of insoluble long-chain triglycerides, phospholipids, and cholesterin esters. Human lipases include a pre-duodenal form (lingual and gastric) and an extra-duodenal form (pancreatic, hepatic, endothelial and lipoprotein-lipase); the pancreatic lipase is inhibited by the biliary salts but can be activated in the presence of the pancreatic protein colipase that with the lipase form a complex that is necessary for the enzymatic activity. Other forms of lipase are present in the hepatocytes [4] and endothelium [5].

Pancreatic enzymes (PE) after their synthesis in the pancreatic acinar cells are transported as a pro-enzymes form in the zymogen granules and secreted in the pancreatic ducts and finally into the duodenal lumen. Brush border enterokinases provide for their

* Corresponding author. Department of Physics, University of Salerno, Salerno, Italy.
E-mail address: pcavallo@unisa.it (P. Cavallo).

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activation. After completing their duty PE are filtered through the kidneys, and about 25% of amylases and 100% of lipases are reabsorbed in the renal tubules. 25% of Amylases are lost in the urine, 75% metabolized probably in the liver while lipase is completely metabolized in the kidney.

The increased blood level of the PE can be due to increased pancreas release, decreased kidney clearance and/or to increased release of PE from non-pancreatic tissues. The increased PE levels in the blood can also be due to pancreatic duct obstruction and mild direct damage of the acinar cells that determines PE leakage from the cell basolateral membrane. Some other conditions may also cause increased levels of PE in the bloodstream, including diabetic ketoacidosis, biliary and ovary cancer, pancreas divisum, hepatitis, liver carcinoma, macroamylasemia, genetic mutations, celiac disease, and inflammatory bowel diseases.

A study [5] in German patients showed that increased PE activities occurred in 8% of hospitalized patients with non-pancreatic diseases, but only in a few cases there have been found pancreatic abnormalities such as chronic pancreatitis and small cystic lesions.

Among those other causes, the Benign Pancreatic Hyperenzymemia (BPH) is a syndrome characterized by a chronic increase of serum pancreatic enzymes in the absence of pancreatic disease [6] The enzyme levels show considerable variation from one test to another, showing even marked day-to-day variations along the life, and also enzyme normalization can be seen [7,8]. Only one study addressed the possible genetic origin of such a condition but was unable to find an association with *PRSS1* and *SPINK1* mutations, as it has been demonstrated in hereditary pancreatitis [9].

The exact prevalence in the general population of the pancreatic hyperenzymemia, and in particular of benign pancreatic hyperenzymemia is unknown.

Electronic Health Records (EHR) of General Population (GP) can provide useful information [10–12], with significant value because complementary, wider and more geo-localized than hospitalized patient EHR.

The present study aims to evaluate the frequency and characteristics of unexplained pancreatic hyperenzymemia in a large cohort of individuals who underwent repeated assays for increased PE levels in a referral laboratory centre.

Methods section

The study is a retrospective observational study.

Data of PE testing of the present study were drawn from the database of a regional referral laboratory centre affiliated to the National Health System of the Province of Salerno, Southern Italy, which encompasses about 1.1 M residents. Data on such testing from a single laboratory had been collected on a computerized database from 2011 to 2015. The laboratory Electronic Health Records (EHR) included all the demographic, diagnostic and laboratory tests data.

We extracted from the laboratory EHR all subjects who had undergone Pancreatic Enzyme (PE), Amylase and/or Lipase assay for routinely check-up from January 2011 to December 2015. We recorded a code number identifying each patient, the ICD 9-CM code when available, gender, age, amylase and lipase levels, isoamylase levels, amylasuria and other laboratory tests. The isoamylase levels and amylasuria were rarely documented, as GPs rarely requested them. We obtained a cohort of 4964 patients which requested a total of 9644 Amylase and 4030 Lipase assays. Of these, 1688 patients had requested three or more times Amylase and/or Lipase during the study period, for a total of 6422 Amylase (66.5% of total Amylase assays), and 2759 (68.4%) Lipase assays; in 2623 cases both the enzyme assays were requested at the same time.

From them, we selected only those who had a persistent increased PE, at least two times the upper normal, which constituted our study population.

We matched the data with the associated International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) from the GPs database including also imaging data and, whenever available, with a positive diagnosis.

The participants gave written consent for the use of anonymous personal and laboratory data collected was obtained at the moment of the blood test. The relevant Ethical Committee (Comitato Etico Campania Sud) gave its approval, with registration number 83 released on 2016/10/05. We collected the clinical data of included patients from the GPs database by matching our series patients' codes. According to the Italian regulatory laws 571/2013 and 572/2013, the need for patients consent was waived. The GPs sent the patients with repeated increased amylases to a gastrointestinal (GI) specialist visit at the local University Hospital. Data from the clinical records were collected and analyzed. Patients with unexplained PE hyperenzymemia were invited to a routine follow-up visit during which they also underwent a psychological interview. The data we present in the study are related to the last follow-up visit, performed in 2017.

As per routine, the patients with chronic diseases undergo a clinical psychological interview and the Mini International Neuropsychiatric Interview to assess DSM-5 depressive features (MINI) made of simple 6 questions. The MINI [13] questionnaire, presented in the Supplementary Materials, Table S2, is self-administered instrument that can be easily administered by physicians and GPs. It evaluates the DSM-5 specifier "with depressive features". A point is scored every time a patient answers yes to a question. In questions 2, 4 and 5, a point is scored if the patient answers yes to either a or b. If the total number of points is equal to or greater than 3, the patient presents a probable (hypo-) manic episode with depressive features. Moreover, we asked the patients to write a few lines about their feelings about their disease.

In our University Hospital clinical, diagnosis and relevant records of patients seen in the outpatient clinic are summarized in the hospital database upon completion of the visit, while the paper clinical records also contain lab test and details of the clinical outcome.

Concerning the statistical analysis, categorical variables were expressed as a frequency. Differences in frequencies between males and females were calculated using the $\chi 2$ test. Data were analyzed using an IBM SPSS 19 software.

Results

During the period of observation, the laboratory performed 2.309.921 blood tests for 577.251 admittances, which included a total of 4964 patients tested at least once for PE assays. The data of the 4964 patients with PE tests performed from 2011 to 2015 were analyzed. All participant at the time of blood tests gave their consent to future analysis of their data. Gender was equally represented, 2260 (45.5%) males and 2704 (54.5%) females. Table S1, in the Supplementary Materials, shows the age and gender distribution of all patients tested for PE, and Fig. 1 shows the flowchart of the cohort under study.

We excluded 3276 patients who had less than three consecutive blood test for PE over a period of at least two years, keeping the remaining 1688 subjects. Of these 437 (25.9%) had altered PE and in particular, the data matched with the ICD 9-CM code, allowed to identify 395 cancer/pancreatic disease and 42 with an unexplained persistent PE increase over time.

The hospital records showed that all patients at the

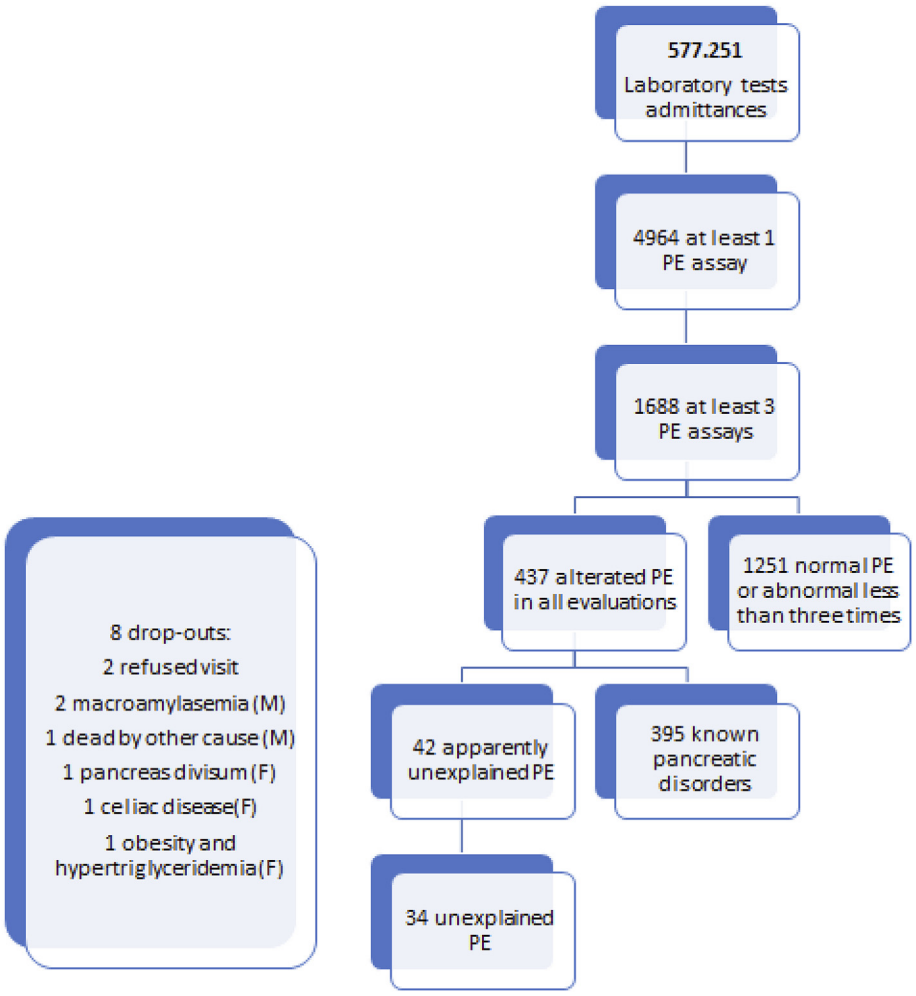

Fig. 1. Flowchart of the cohort under study.

gastrointestinal specialist visit underwent through work −up for increased PE, including the presence of macroamylasemia, by assessing the 24-h urine collection amylase level, the amylase isoenzymes levels, and pancreatic imaging.

The patients with a cause for the increased PE either pancreatic diseases, macroamylasemia, salivary amylase increase, renal insufficiency were excluded from further analyses.

Table 1 shows the distribution between males and females and shows no gender-related difference in patients with altered PE.

We focused our attention to the group of 42 patients with apparently unexplained increased PE, collecting their clinical records at the follow-up visit in the outpatient clinic at the local Gastrointestinal Diseases Unit, or when this was not possible, with a phone interview assessing their health status. The follow-up time was between 2 and 6 years. The clinical records showed that all 42 patients with a persistent increase of PE had undergone over time a complete work-up for pancreatic diseases, including the urinary test for amylasuria, at least one tomography or magnetic resonance and several US scans. Eight patients were excluded: one had died at the age of 87 for cardiovascular problems and no known pancreatic disease; two refused to undergo follow-up visits. One woman had undergone a Magnetic Resonance Imaging (MRI) test that eventually showed a pancreas divisum, while another reported that she eventually received the diagnosis of celiac disease. In two male patients macroamylasemia was present and in both the lipase level was few units above normal (no clinical significance). One woman presented obesity (BMI 30) and hypertriglyceridemia. Therefore, we evaluated data of the 34 patients with increased PE in which no pancreatic disease or other relevant disease involving pancreatic impairment was known at the moment of the phone call. Thus, we found a prevalence of 2% (34 patients out of 1688 subjects who underwent PE three or more times during the study) of unexplained altered PE. One patient reported that the first occurrence of increased PE was detected at the local Emergency Unit for drug-induced (azathioprine therapy for psoriasis) acute pancreatitis. Although he never took the medication again, and was accurately

Table 1
Gender distribution of participants, also divided for the number of PE test and the diagnosis.

Group	Males (%)	Females (%)	Total	p (M vs F)
At least 3 PE tests along the study	851	837	1688	0.913
Three altered PE	254 (29.8%)	183 (21.9%)	437 (25.9%)	0.483
Final unexplained diagnosis	16 (1.9)	18 (2.1%)	34 (2.0%)	0.942

investigated over five years looking for pancreatic diseases, including ERCP and EUS, no clues of chronic pancreatic disease or inflammatory bowel disease were found despite a mild increase of the level of PE. We believe that he likely had acute pancreatitis overlapping an existing chronic idiopathic pancreatic hyperenzymemia and thus he was included in the series of the benign PE hyperenzymemia. In the group of 34 patients with unexplained increase of PE, despite a number of laboratory and imaging investigations (in 30/34 both CT scan and MRI, in 26/34 also EUS, in 33/34 repeated abdominal US scans, in 30/34 fecal elastase assay) after a mean follow-up time of 4 ± 0,7 years no pancreatic diseases were detected.

Table 2 shows that the vast majority of them (24/42, 57.1%) were in the age group 51–75, more women than men (11 M, 13F). Clinical records showed that they were mostly asymptomatic, although two women were affected with irritable bowel syndrome type C. Nevertheless, they all had undergone a minimum of four imaging investigations each and several laboratory tests. There was an oscillation in their serum PE levels among the tests, but we could not identify any particular difference between the cases, time of blood withdrawal, or the season.

Of the thirty-four patients who underwent the follow-up visit, mostly during the structured psychological interview, emerged that they received some information from the GI specialist they saw at least once.

The clinical psychological interview showed that no one was affected by major anxiety or depressive disorder. However, all of the patients claimed to be seriously worried about the health status. The MINI score was 1 ± 1,25 (range 0–4) with 4 patients out of 34 scoring >3, suggesting the probable (hypo-) manic episode with depressive features. The interview revealed that the vast majority was not persuaded about the benignity of their condition, and mostly worried about the evolution of the PE alterations.

They were in the vast majority (29/34) scared about the possibility to have fatal pancreatitis, and 30/34 quitted smoke and claimed to drink less than two glasses of wine per week, mainly in the social gatherings. All the smokers quitted smoking upon GPs advice. The smoking habit was perceived as a condition of high risk for pancreatic cancer.

Also, 29/34 claimed to follow a 'protective diet' by avoiding fatty food, cured meat, pepper and spices, and junk food even if a physician/dietitian never prescribed it. All of them claimed a reduced quality of life because of diet limitations, the need of numerous investigations, and the fear of a possible pancreatitis event, in particular during a journey (that 12% of them claimed to avoid).

Discussion

The existence of fluctuating PE increase in the absence of a specific disease is a challenge in the clinical practice. To our knowledge, the prevalence of the benign PE increase in the general population, also named Gullo syndrome from the name of the researcher that first described adult and children case series [6,7,14,15], is unknown. However, it is considered a rare disease in Eastern countries, worth a clinical case description [16].

Our data indicate that the prevalence of benign chronic PE increase among subjects underwent to a blood test for multiple PE testing along the time is 2%.

The studies so far published demonstrate that in most cases a pancreatic disorder cannot be demonstrated [8]. Recently, Amodio et al. found that 50% of patients of their series with fluctuating PE increase showed to accurate imaging, a pancreatic disease [17]. Pezzilli et al. found that only half of the patients with fluctuating PE increase were affected by a benign hyperenzymemia [18]. However, the latter data are in evident contrast with those published by Galassi et al. who were unable to find a pancreatic/salivary disorder in 88,4% of their patients. The contrast might be explained by the different entry criteria of the studies, as Amodio et al. included symptomatic patients and Galassi only asymptomatic CT scan/MR-negative patients, while Pezzilli included patients with fluctuating PE levels and a 'normal' US scan who were, after the entry into the study, examined with other imaging or endoscopic techniques. The approach of our study was different from the others, as we identified the subjects with the increased PE at repeated tests, excluded the symptomatic ones or with cancer and pancreatic disease, and analyzed only those with an inexplicable PE increase.

Therefore, the novelty and the strength of the present study is that we identified patients with benign PE hyperenzymemia among those undergoing routine laboratory tests, while all the other studies so far published deal with patients seen in a Tertiary Centre for Pancreatic Diseases [8,17,19,20]. Furthermore, the inclusion of the follow-up visit allowed us to be sure of the correct diagnosis. Our series corresponds in its characteristics to that presented by Galassi et al. in 2014 [8], with the difference that Galassi studied a large number of patients extensively referred to an Italian Pancreatic Disease Referral Centre, thus exploring a selected group, while we used available EHR data from GPs, thus exploring a general population sample.

The use of Electronic Health Records has shown to be a simple, convenient and reliable instrument to study the epidemiology of the general population, also as previously shown [11,12,21]. In the present case, they have also been a useful instrument to identify specific clinical patterns.

The limitation of our study is that, as we retrospectively analyzed data from a laboratory database, we might have missed some cases in the general population that did not undergo laboratory testing of PE, or if they did, we could not have access to their data. The possibility exists that those who showed an increase in PE once may be pressed to repeat the test over time, while some of the individuals whose PE resulted within the normal range likely did not repeat the test over the observation period. Therefore, the prevalence of the condition might be different than that here reported. However, the GPs' database when matched with our series

Table 2
Gender distribution of participants, also divided for the number of PE test and the diagnosis.

Age Range	All Multiple altered hyperamylasemia and hyperlipemia number (n = 437)		Benign Pancreatic hyperenzymemia (Gullo) (n = 42)				
			absolute		percent		Chi-square M vs. F (P)
	M	F	M	F	M %	F %	
0–25	8	3	1	1	12.5%	33.3%	0.44
26–50	32	21	3	5	9.3%	23.8%	0.15
51–75	145	101	11	13	7.6%	12.8%	0.17
75+	69	58	4	4	5.8%	6.9%	0.80
TOT	254	183	19	23	7.5%	12.5%	0.08

patients' codes were unable to find any increased levels of benign PE in the other patients present in their database, and the majority of individuals with normal PE repeated the PE testing over time as per their check-up list. Moreover, the lack of amylase in urine determination represents a limitation of this study because the presence of macroamylasemia cannot be ruled out in these patients having chronic non-pathological hyperenzymemia.

Our results indicate that benign PE hyperenzymemia (BPH) is a relatively uncommon condition and, likely because of this reason, poorly known by patients and GPs. Patients with benign PE hyperenzymemia perceive their condition as a relevant disease. The vast majority feels that a Damocles sword hangs over their heads and wish to be frequently investigated and reassured. Our findings are different from those reported in 2015 by Pezzilli et al. [20] that showed that 51 patients scored the SF12 and GHQ-12 questionnaires not differently from the reference population. The possible explanations for the difference are in the use of different instruments for evaluating well-being, in the fact that 7/55 patients had a relative with a similar diagnosis, and that may be a reassuring circumstance, and in the fact that these long-standing CNPH patients (mean duration 11 years) were followed in a tertiary Centre for Pancreatic Diseases, thus having a strong, qualified support to help them understand and deal with their condition, while our patients were, from a certain point of view, left to themselves. In fact, in the best case, they had initially received limited information by the GPs regarding the benignity of their condition.

Our data add a piece of the information to the small data on the prevalence of benign PE hyperenzymemia and points out to the fact that there is an unmet need for a more informed and reassuring follow-up for people with benign pancreatic hyperenzymemia. Moreover, our data indicate that the practice of including the amylase assay in the work-up package for routine testing for workers and insurance reasons in the absence of a clear indication is not necessary, and likely cause a waste of money and time.

The heavy impact of this condition on the well-being of the patients, with nearly all of them scared and worried for their health, may suggest that further studied should be performed, analyzing different population settings, to confirm or modify either the prevalence and the psychological impact which we have found in the present study. Finally, the further studies should also address the question of how to manage the patients with the BPH, which, even if not a disease but a condition, imposes a heavy burden on their quality of life.

Author contributions

Conceptualization, P.C. and C.C.; Methodology, P.C. and C.C.; Software, P.C. and I.S.; Validation, all the authors; Formal Analysis, C.C. and F.Z.; Investigation, C.C., L.C. and F.Z.; Resources, P.C., I.S. and M.D.S.; Data Curation, L.C. and I.S.; Writing - Original Draft Preparation, C.C.; Writing - Review and Editing, C.C., F.Z. and P.C.; Funding Acquisition, P.C.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.03.003.

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