



The national institutes of health's approach to address research gaps in pancreatitis, diabetes and early detection of pancreatic cancer

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Purpose of review

Diseases of the pancreas are a broad spectrum of conditions resulting from metabolic, inflammatory, and neoplastic processes (pancreatitis, pancreatogenic diabetes, and pancreatic cancers). Pancreatic diseases cause significant morbidity, mortality, and cost.

Recent findings

Research progress in diseases of the exocrine pancreas (chronic pancreatitis [CP], pancreatogenic diabetes mellitus, and pancreatic cancer) has been hampered by the disorders' heterogeneity, the limitations of previous small cross-sectional studies, the inability to safely obtain pancreatic tissue for study, and the lack of structured epidemiology tools, genetic testing, and biomarker development.

Summary

Given the increasing incidence and prevalence of CP and its complications, high mortality rate, and associated healthcare cost, the National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute funded the Consortium for the study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) to identify research gaps and foster multidisciplinary collaborations to better diagnose, characterize and manage CP and its sequelae and to understand the diabetes/pancreatic cancer association.

The studies undertaken by the CPDPC are described in other articles in this journal's issue.

Keywords

chronic pancreatitis, consortium for the study of chronic pancreatitis, diabetes and pancreatic cancer, diseases of the exocrine pancreas, National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health funding of research, pancreatic cancer, pancreatogenic diabetes mellitus, research progress

INTRODUCTION

Diseases of the pancreas are a broad spectrum of conditions resulting from metabolic, inflammatory, and neoplastic processes (pancreatitis, pancreatogenic diabetes, and pancreatic cancers). Pancreatic diseases cause significant morbidity, mortality, and cost [1[•]].

The economic burden from pancreatic diseases has increased over the past several years in the United States. Recent estimates from 2014 hospital inpatient data showed acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic ductal adenocarcinoma (PDAC) accounted for \$2.6 billion, \$134 million, and \$688 million in aggregate costs, respectively [1[•],2].

PDAC is the third leading cause of cancer mortality in the United States with an estimated 55,440 new diagnoses and 44,330 deaths in 2018 [3,4].

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KEY POINTS

- Diseases of the pancreas are a broad spectrum of conditions resulting from metabolic, inflammatory, and neoplastic processes, causing significant morbidity, mortality, and cost.
- Research progress in diseases of the exocrine pancreas has been hampered by the disorders' heterogeneity, the limitations of previous small cross-sectional studies, the inability to safely obtain pancreatic tissue for study, and the lack of structured epidemiology tools, genetic testing, and biomarker development.
- The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Cancer Institute (NCI) jointly and through other initiatives, have supported the scientific community to undertake a comprehensive clinical, epidemiological, and biological characterization of patients with CP (including those with ARP) to gain insight into the pathophysiology of CP and its sequelae: chronic pain, pancreatic insufficiency, T3cDM, and the diabetes/pancreatic cancer association.
- Multiinstitute and multidisciplinary collaboration will bear fruit in the near future by providing the environment for innovative and systematic approach to the study of pancreas diseases.

PDAC is also a leading cause of mortality among all cancers of the digestive system [4] and is estimated to become the second leading cause of cancer-related death in the United States by 2030 [5]. Early detection of pancreatic cancer leads to better patient survival. Whereas the 5-year survival of all surgically resectable PDAC is 20–30% [6,7] the 5-year survival of patients with less than a 2 cm tumor has been reported as 30–60% and for tumors less than 1 cm the 5-year survival is 75% [8]. Small tumors are usually found incidentally or as a consequence of repeated surveillance of high-risk groups, but the identification of high-risk groups in the general population has been a challenge. Principal challenges to developing an early detection program for sporadic PDAC are the data paucity of an identified high-risk group; limited availability of biospecimens; dearth of biomarkers for PDAC; and inability of imaging techniques to identify early PDAC. One known high-risk group for sporadic PDAC are older patients (>50 years) with glycemically defined new-onset diabetes [9]. Patients with new-onset diabetes are at elevated risk of PDAC with a cumulative incidence rate over 3 years of 0.85% and are 6–8-fold higher-risk of being diagnosed with PDAC within 3 years of developing new-onset diabetes [10].

AP is one of the most frequent gastrointestinal causes of hospital admissions in the United States. In 2012, AP accounted for 330,561 emergency department visits and 239,839 subsequent hospitalizations from emergency department visits [4]. CP is characterized by chronic abdominal pain, frequent exacerbations, and exocrine/endocrine insufficiency [11].

CP is a progressive, debilitating, incurable disease that involves continuous inflammatory and fibrotic changes [12] of the exocrine pancreas resulting in permanent structural damage, and which can lead to impairment of both endocrine and exocrine functions. The annual incidence rates reported worldwide are roughly similar in all countries and range from 5 to 14 per 100,000 individuals, with a prevalence of approximately 30–50 per 100,000 individuals [13,14]. The most recent studies seem to indicate an increasing incidence of CP in the past decade [15]. Although the incidence of CP is lower compared with AP, it significantly affects patients' quality of life [16] and represents a risk factor for PDAC.

Regardless of the underlying etiology for CP, the development of end-stage disease is characterized by multiple complications including pain, pancreatic insufficiency (endocrine and/or exocrine), metabolic bone disease, and potentially PDAC. The risk of PDAC increases progressively with the duration of the disease and is highest in patients with CP accompanied by secondary, or type 3c, diabetes (T3cDM). Indeed, CP is the strongest identified risk factor for pancreatic cancer and increases the risk at least 13.3-fold [17]. Moreover, patients with both CP and diabetes have up to a 33-fold increased risk of pancreatic cancer [18].

Despite this devastating clinical course, the factors that determine the initiation of the disease, its progression to severe fibrosis, and its possible transformation into malignancy are all unclear and methods to screen patients at high risk for the development of pancreatic carcinoma are not well established or practiced uniformly [19].

NATIONAL INSTITUTES OF HEALTH'S APPROACH TO ADDRESS RESEARCH GAPS IN PANCREATIC DISEASES

National Institutes of Health sponsored workshops and conferences to identify gaps in pancreas research

A series of workshops and conferences to identify research gaps and foster multidisciplinary collaborations to better diagnose, characterize and manage CP and its sequelae, were organized by the National

Cancer Institute (NCI) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) following input from multiple patients advocacy groups, professional societies and Advisory Councils to NCI and NIDDK.

In 2009 The National Commission on Digestive Diseases proposed several goals related to the need for further research in pancreatic diseases [20,21], prominent amongst them, to determine the biological and genetic factors involved in the pathogenesis of CP, with particular emphasis on mechanisms of tissue necrosis, fibrosis.

NIDDK sponsored a workshop in June 2012 where lead scientists and clinicians reviewed the state of the art in areas of research and gaps in research for the pancreas. These experts stressed the need for further basic and translational studies in CP to identify strategies and therapeutic targets to reduce the burden of disease. Another workshop, co-sponsored by NIDDK and NCI, was held in June 2013 and highlighted the risk factors which link CP, diabetes, and pancreatic cancer. An initiative in this area was believed to encourage more applications and increase the NIDDK and NCI portfolios in this under-represented area of important research [18].

The Recalcitrant Cancer Research Act of 2012 (Public Law 112–239, §1083) [22] calls upon the NCI to ‘develop scientific frameworks’ that will assist in making ‘progress against recalcitrant or deadly cancers’. PDAC is a recalcitrant cancer as defined by its five-year relative survival rate of less than 5%. The limited early diagnostic or therapeutic approaches for patients with PDAC have provided a stimulus for the evaluation of new and missed opportunities that could now be applied to the existing portfolio of pancreatic cancer research to make more substantial progress. In February 2014, NCI published a Scientific Framework for PDAC, which gave specific recommendations. These were based in part on the recommendations from a panel of extramural scientists convened by NCI in October 2012 and from an interdisciplinary meeting on June 2013 co-sponsored by NIDDK, NCI, and the Pancreatic Cancer Action Network: NIDDK-NCI Pancreatitis-Diabetes-Pancreatic Cancer Workshop [18]. In the area of early detection of pancreatic cancer, the NCI Scientific Framework for PDAC recommendations included: (1) development of an in-depth understanding of the biological and clinical relationship between PDAC and diabetes mellitus of recent onset; (2) evaluation of longitudinal screening protocols, concomitant with the development of new molecular and imaging biomarkers for patients at high risk for PDAC (because of genetic factors or the presence of mucinous pancreatic cysts) who could be candidates for early surgical intervention.

The consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer clinical centers, an National Institutes of Health funded initiative to promote clinical research in diseases of the pancreas

From these workshops and meetings, the NCI and NIDDK developed a request for applications (RFA) to support the development of clinical resources that would address some of these recommendations [23,24]. The result of the RFA was the establishment in 2015 of a multidisciplinary consortium formed by a Coordination and Data Management Center (CDMC) and several clinical centers (CC) of excellence: the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer Clinical Centers (CPDPC). In 2019 in view of accomplishment of the initial CPDPC and following advice by an external scientific evaluation panel, the directors of the NCI and NIDDK issued funding opportunities for the continuation of the CPDPC for another 5 years of funding. Table 1 for list of participating centers [25,26].

The CPDPC is formed by multidisciplinary teams composed of members from the CCs and the CDMC to undertake a comprehensive clinical, epidemiological, and biological characterization of patients (children and adults) with CP including those with Acute Recurrent Pancreatitis (ARP) to gain insight into the pathophysiology of CP and its sequelae: chronic pain, pancreatic insufficiency, T3cDM, and the diabetes/pancreatic cancer association. The teams are also undertaking studies on the development of pancreatic cancer in newly diagnosed diabetic patients.

The overriding two objectives of this research program are to pursue clinical research (1) on CP including those with (ARP) by identifying and characterizing a large cohort of pediatric and adult patients with CP and ARP to encourage translational research focusing upon elucidating the pathogenesis that will provide the basis for understanding the natural history and developing improved means of diagnosis, treatment and clinical management of CP and its sequelae including chronic pain and pancreatic insufficiency and (2) on pancreatic cancer and pancreatogenic diabetes mellitus (T3cDM) and their pathogenic interrelationships, by identifying and following a cohort of newly diagnosed diabetic patients.

The CPDPC’s investigators represent the largest accumulation of pancreatic research expertise in the United States, working from top academic CCs distributed across the United States, providing a comprehensive ‘catchment’ area to bring a diverse patient population to the studies of the CPDPC.

Table 1. List of participating Centers in the Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC), in response to funding opportunities issued by NCI and NIDDK in 2014 and 2019

Clinical Centers	Principal Investigator(s)	CPDPC group
Baylor College of Medicine, Houston, TX	Fisher, William	1 & 2
Cedars-Sinai Medical Center, Los Angeles, CA	Pandol, Stephen; Goodarzi, Mark	1 & 2
Indiana University, Indianapolis, IN	Fogel, Evan	1 & 2
Kaiser Foundation, Oakland, CA	Van Den Eeden, Stephen	1
Mayo Clinic, Rochester, MN	Chari, Suresh; Topazian, Mark	1
Mayo Clinic, Rochester, MN	Vege, Santhi S; Petersen G	2
Ohio State University, Columbus, OH	Conwell, Darwin; Hart, Phil	1 & 2
Stanford University, Palo Alto, CA	Park, Walter; Habtezion, Aida;	1 & 2
University of Florida, Gainesville, FL	Forsmark, Christopher; Cusi, Kenneth; Hughes, Steven	1 & 2
University of Iowa, Iowa City, IA	Uc, Aliye	1 ^a & 2 ^a
University of Minnesota, Minneapolis, MN	Bellin, Melena; Beilman, Gregory	2
University of Pittsburgh, Pittsburgh, PA	Yadav, Dhiraj; Whitcomb, David	1
University of Pittsburgh, Pittsburgh, PA	Yadav, Dhiraj; Brand, Randall E	2
University of Texas MD Anderson Cancer Center, Houston TX	Suresh Chari; Anirban Maitra	2
Coordination and Data Management Center	Principal Investigator(s)	CPDC group
MD Anderson Cancer Center, Houston, TX	Feng, Ziding; Maitra, Anirban	1
MD Anderson Cancer Center, Houston, TX	Ying Yuan; Liang Li; Maitra, Anirban	2

^aPediatric CC, serving as point of contact for a network of 24 pediatric centers across the United States, Canada, Australia, and Israel

In pursuing the research objectives of the CPDPC, as outlined in the published RFAs and developed by the investigators, the consortium is organized into 4 working groups around the main research objectives under the leadership of co-chairs C. Forsmark and S. Pandol:

Adult Chronic Pancreatitis Working Group (Chairs: D.L. Conwell; D. Yadav)

Pediatric Chronic Pancreatitis Working Group (Chairs: A. Uc; M.E. Lowe)

Diabetes Mellitus Pancreatic Ductal Adenocarcinoma Working Group (Chairs: S.T. Chari, A. Maitra)

Type3c Diabetes Mellitus Working Group (Chairs: M. Goodarzi, P. Hart)

With significant cross-fertilization across the 4 working groups, the consortium's investigators have implemented 3 major longitudinal studies and a cross-sectional study to standardize the diagnosis of CP and ARP and characterize T3cDM in association with pancreatic cancer, as well as multiple ancillary studies (see other articles in this issue of *Current Opinions in Gastroenterology*).

The CPDPC Investigators have proposed over 50 ancillary/associated studies to understand CP progression and conduct discovery and validation studies of promising biomarkers for diagnosis and prognosis of CP, mechanistic studies that provide insight into CP pathogenesis, microbiome studies

to understand differences in patients with CP when compared to controls or pancreatic cancer, and genetic studies that may provide further insight into CP susceptibility and progression. Ultimately, this will support new diagnostic and therapeutic approaches for CP and its sequelae. The ancillary studies by the CPDPC investigators additionally include associated studies on the identification of high-risk groups for pancreatic cancer among patients with newly diagnosed diabetes; microbiome studies; genetic studies; and epidemiological studies on the diabetes/pancreatic cancer association.

In addition to the ongoing prospective clinical studies, a major collaborative effort within the Consortium has been the establishment of an annotated repository of bio-specimens (blood, pancreatic and duodenal juice, stools and when feasible pancreatic tissue) to allow for the identification and validation of biomarkers for risk stratification and/or early detection for pancreatic diseases as well as early detection of pancreatic cancer.

Through the acquisition of a cohort of well-characterized patients and associated biospecimens, the CPDPC provides the resources and collaborative opportunities necessary for achieving many of the research objectives identified in the strategic plans of the participating institutes.

The Consortium also provides an environment that fosters internal and external collaborations through ancillary studies, which in the future will provide new information on the epidemiology, pathogenesis, and treatment of CP and its sequelae, in both in children and adults, as well as diabetes and pancreatic cancer.

The study of the association between pancreatic cancer and diabetes is being addressed in the CPDPC through the study of New-Onset Diabetes being conducted through the DM-PDAC Working Group. In collaboration with the Pancreatic Cancer Action Network (PanCAN), the Early Detection Initiative (EDI) was developed as an interventional trial. The EDI study is designed to evaluate if imaging at the time of new onset diabetes results in earlier detection of PDAC. The goal of the study is to improve the detection of sporadic PDAC when surgical intervention is possible. In addition, the EDI study will contribute biospecimens (serum and plasma) to the new-onset diabetes study for future, retrospective biomarker studies in a collaborative effort with the CPDPC.

Although pancreatogenic DM is a simple term, the disease includes diverse pathophysiological differences according to the underlying pancreatic disease, as previously described for CP, pancreatic cancer, and cystic fibrosis [27]. Pancreatogenic DM secondary to AP is likely the most common diagnosis in view of the relatively higher prevalence of AP [28]. A previously unrecognized long-term sequela, besides exocrine pancreatic insufficiency and recurrent episodes of pancreatitis in up to 20% of patients [29,30] is the development of transient hyperglycemia and frank new onset diabetes, with a cumulative incidence ranging from 23% to 40% [31,32]. To undertake a prospective longitudinal observational clinical study to investigate the incidence, etiology, and pathophysiology of diabetes following AP with a particular emphasis on the auto-immune processes that result in Type 1 Diabetes (T1DM), in the fall of 2020 the NIDDK formed a collaborative network of 10 CC and one data coordinating center, referred to as Type 1 Diabetes after Acute Pancreatitis Consortium, to collaboratively address a number of these knowledge gaps [33,34].

The main objective of this research program is to undertake an observational cohort study of patients with AP to investigate the incidence, etiology, and pathophysiology of diabetes following AP with a particular emphasis on the auto-immune processes that result in T1DM.

CONCLUSION

The NCI and NIDDK, jointly and through other initiatives, have supported the scientific

community to undertake a comprehensive clinical, epidemiological, and biological characterization of patients with CP (including those with ARP) to gain insight into the pathophysiology of CP and its sequelae: chronic pain, pancreatic insufficiency, T3cDM, and the diabetes/pancreatic cancer association. Although this multi-institute and multidisciplinary collaboration will bear fruit in the near future by providing the environment for innovative and systematic approach to the study of pancreas diseases, it has already changed the prospect of gaining significant knowledge to impact the natural history of CP and the diabetes/pancreatic cancer association.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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