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Wicks, Mary M.; Barr, Elizabeth L.M.; Maple-Brown, Louise

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Wicks Mary (Orcid ID: 0000-0002-7342-6446)

Title: Pancreatitis and Post-Pancreatitis Diabetes in Central Australia

Mary Wicks[1], Elizabeth LM Barr[2,3], Louise Maple-Brown[2,4]

Affiliations:

1. Menzies School of Health Research, Alice Springs

2. Menzies School of Health Research, Charles Darwin University, NT, Australia

3. Baker Heart and Diabetes Institute, Vic, Australia

4. Department of Endocrinology, Royal Darwin Hospital

Author Roles:

MW: General Physician and Doctoral Candidate based in Alice Springs

EB: Senior Research Fellow at Menzies School of Health Research and Public Health Epidemiologist at Baker Heart and Diabetes Institute

LMB: Senior Principal Research Fellow Menzies School of Health Research and Head of Endocrinology at Royal Darwin Hospital

Author contributions:

MW conceived the study, acquired the data, analysed, and interpreted the data, drafted, and revised the manuscript. EB and LMB contributed to study design and provided critical review and assistance with data analysis and interpretation. MW, EB, LMB agreed to the published version of the manuscript.

Corresponding Author:

Dr Mary Wicks, Menzies School of Health Research, W & E Rubuntja Building,

Alice Springs Hospital Campus, PO Box 1294, Alice Springs, NT, 0871

Mary.Wicks@Menzies.edu.au, Ph: 08-8959 0111

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Key Words: Pancreatitis, Diabetes, Exocrine Pancreas, Northern Territory, Indigenous Health.

Note on Terminology: The First Nations people of Central Australia refer to themselves as Aboriginal people and this terminology will be used in this paper.

Acronyms:

AP Acute Pancreatitis

ASH Alice Springs Hospital

CAHS Central Australia Health Service

CP Chronic Pancreatitis

DEP Diabetes of the Exocrine Pancreas

PPDM Post-Pancreatitis Diabetes Mellitus

PEI Pancreatic Exocrine Insufficiency

T2D Type 2 Diabetes Mellitus

TCH Tennant Creek Hospital

ABSTRACT

Background

Pancreatitis and diabetes are common among Aboriginal people of Central Australia. The contribution of pancreatitis to the development of Post-Pancreatitis Diabetes-Mellitus (PPDM) is not known.

Aims

To describe among Aboriginal and non-Aboriginal people living in Central Australia, (i) the prevalence and aetiology of Acute (AP) and Chronic Pancreatitis (CP) and, (ii) diagnosis of new onset diabetes after pancreatitis.

Methods

Retrospective medical record review of patients ≥ 15 years admitted to hospitals in the Central Australia Health Service between 2009 and 2018 with pancreatitis. Prevalence as a proportion of the resident population and aetiology of AP and CP were determined. Diagnosis of new onset diabetes after admission with pancreatitis was assessed.

Results

Of the 638 patients assessed, 73% were Aboriginal and 48% female. The annual prevalence in 2009 and 2018 for AP was 171 and 203 per 100 000 persons, and for CP was 206 and 114 per 100 000 persons, respectively. Rates were high in Aboriginal people. Alcohol aetiology was most common in Aboriginal people at (66%) and biliary aetiology in non-Aboriginal people (37%). A diagnosis of diabetes after pancreatitis was detected in 125 of 438 (29%) patients who did not have diabetes diagnosis previously recorded, and 20 of the 22 tested for diabetes-associated antibodies were negative, fitting criteria for PPDM.

Conclusion

Prevalence of AP and CP in Central Australia was higher in Aboriginal than non-Aboriginal people. Few patients with diabetes recorded after pancreatitis had appropriate PPDM diagnostic testing. Inter-disciplinary education on the diagnosis of PPDM is required.

INTRODUCTION

Pancreatitis is a common presentation to Alice Springs Hospital (ASH). Previous studies estimated the prevalence of Acute Pancreatitis (AP) at 120-275 per 100 000 population.[1,2] In both of these studies prevalence of pancreatitis was significantly greater in Aboriginal compared to non-Aboriginal people. These prevalence rates are well above those reported internationally.[3,4] There are no local data regarding Chronic Pancreatitis (CP) prevalence.

Both acute and chronic pancreatitis have a high alcohol-attributable aetiological fraction (>0.8) and are markers of alcohol-related harm.[5] The estimated alcohol consumption in Alice Springs, derived from wastewater data in August 2016, was 45 litres per 1000 people per day. This compared to the national average of 17 litres per 1000 per day.[6] High alcohol consumption and its related harm are a major community and health concern in Central Australia.[7] The total social cost of alcohol use in the Northern Territory in 2015/16 was estimated at $1 386.8 million.[8]

Diabetes secondary to disease of the exocrine pancreas is being increasingly recognised as a significant cause of diabetes mellitus.[9,10] The terminology around this type of diabetes is inconsistent and changing. It has been referred to as Type 3c diabetes. Most recently the term Diabetes of the Exocrine Pancreas (DEP) is used to describe the entities of Post-Pancreatitis Diabetes (PPDM), pancreatic cancer-related diabetes and cystic fibrosis-related diabetes.[11] PPDM can be appreciated on a spectrum of disease moving from AP to recurrent AP and CP with increasing beta cell loss and worsening pancreatic exocrine function.[12] This pathophysiology, involving both endocrine and exocrine pancreatic systems, marks this as a unique type of diabetes with specific aetiologies, diagnostic criteria, symptoms, and

management.[13] The literature points to this type of diabetes being misdiagnosed and poorly managed[14] and it is suspected that this is also the case in Central Australia.

There are limited data on the rates of PPDM among those with a history of pancreatitis. PPDM with Pancreatic Exocrine Insufficiency (PEI) has traditionally been associated with CP[9] but there is increasing evidence that it can also complicate severe acute AP, necrotising and alcohol related AP.[15] The prevalence of DEP with PEI is estimated at 5-10% of diabetes burden,[16] or the same as, or higher than, type 1 diabetes in community settings.[10] It is commonly misdiagnosed as type 2 diabetes (T2D).[9]

Central Australia is currently in the grip of an epidemic of T2D in Aboriginal people, with 40% of Aboriginal people 20 years or older residing in remote communities having a diagnosis of T2D.[17] The current study was conducted in the context of high rates of both T2D and pancreatitis in Aboriginal people. The aims are to describe among Aboriginal and non-Aboriginal people living in Central Australia the prevalence of acute and chronic pancreatitis and their associated aetiologies and characteristics, and to describe new onset diabetes after admission for pancreatitis. Given the known epidemiological differences in diabetes and pancreatitis, between Aboriginal and non-Aboriginal people in this region, data were stratified according to ethnicity.

METHODS

This retrospective study included all episodes of pancreatitis in Aboriginal and non-Aboriginal people aged 15 years or older who were admitted to the Alice Springs and/or Tennant Creek Hospitals from January 2009 to December 2018. The catchment area of the Central Australia Health Service (CAHS) is approximately 1.4 million square kilometres and includes Central Australia and the Barkly regions of the Northern Territory as well as the cross-border regions of South Australia and Western Australia. The estimated residential population 15 years and older in 2016 was approximately 35 100 with 40% of people being of Aboriginal descent.[18] This region is in the lowest quintile of socioeconomic disadvantage in Australia.[19] The Tennant Creek Hospital (TCH) is within the Alice Springs Hospital (ASH) catchment area. Individuals admitted to TCH and transferred to ASH were considered as one episode of care.

Pancreatitis episodes were retrieved from the clinical information system of CAHS using ICD-10 diagnostic codes of K85.0 to K86.1. Episodes for a given individual were collated. A review of the individuals' electronic primary health and hospital medical records held by CAHS was completed. The first recorded episode of pancreatitis was ascertained and aetiology of pancreatitis, any diagnosis of diabetes, pertinent investigations and complications were noted. Each episode within the study period was verified as to its congruence with consensus definitions of acute and chronic pancreatitis (Table 1).[20,21] Diabetes was considered to be present if a glycated haemoglobin (HbA1c) level of 6.5% (48 mmol/mol) or higher on more than one occasion was identified[22] or if the individual was prescribed diabetes medication (except for metformin). For classification of PPDM, HbA1c that were recorded a minimum of 3 months after the episode of pancreatitis were considered. This time delay is to ensure that the HbA1c level is not reflecting hyperglycaemia associated with the episode of pancreatitis itself or associated therapies. PPDM diagnosis also required negative diabetes-

associated antibodies.[11] PPDM with Pancreatic Exocrine Insufficiency (PEI) was defined as a diagnosis of PPDM with a Faecal-Elastase Test of < 200 ug/g.[25]

The year of diabetes diagnosis and whether it pre-dated or post-dated the first episode of pancreatitis was noted. Five hundred and forty-four episodes of pancreatitis and 188 individuals were excluded from the study as they did not meet standard criteria for pancreatitis (Figure 1). Readmissions with the same diagnosis within 30 days were not counted as discrete episodes due to the high rates of discharge against medical advice and subsequent readmission.[23]

The aetiology of pancreatitis was considered (i) biliary, if radiological imaging demonstrated cholelithiasis, choledocholithiasis, or obstruction of, the biliary tract, (ii) alcohol, if there was a documented history of chronic alcohol abuse and alcohol-related harm, after excluding other common causes, (iii) other, if there were abnormal serum triglycerides or calcium levels, use of implicated medications, infective conditions or other medical causes accepted in the literature as potential aetiologies[24] and were not of biliary or alcohol aetiology and, (iv) unknown, if there was no obvious aetiology or inadequate work-up to elucidate a cause. Only one aetiology was allocated to an individual. If there was more than one aetiology in an individual with multiple episodes of pancreatitis, the dominant one was documented. For example, an episode of biliary disease in an individual with multiple alcohol-related episodes was considered as alcohol.

Statistical analysis

Data were collected by a single researcher (MW), utilising predefined codes and analysed with STATA v.16 (StataCorp Statistical Software. TX, USA, 2019). Annual prevalence rates per 100 000 persons for acute and chronic pancreatitis were calculated based on hospital episode data. Population denominators were based on estimates from the 2011 or 2016 Australian population census data.[18] Data on patient characteristics were assessed for normality and comparisons between Aboriginal and non-Aboriginal people were performed using Pearson's chi-square test and Student's t-test for parametric data and Mann-Whitney U test for non-parametric data. Results are reported as *n* (%), mean and standard deviation or median with interquartile range. This project was discussed with the Indigenous Reference Group of the Diabetes Across the Lifecourse Partnership. Ethics approval was granted by the Central Australian Human Research Ethics Committee (HREC) (CA-19-3521) and Charles Darwin University HREC (H21051).

RESULTS

A total of 1563 episodes of pancreatitis in 638 individuals were verified as per diagnostic criteria (Table 1) and were included in this analysis (Figure 1). Aboriginal people represented 73% and females 48% of the cohort. The mean age at first episode of pancreatitis was 42 years for Aboriginal people and 49 years for non-Aboriginal people ($p<0.001$).

Of the 638 individuals who were admitted between 2009-2018, 495 (78%) first presented with acute pancreatitis and 143 (22%) with chronic pancreatitis. More than half of all episodes were recurrent although this varied greatly between individuals with a range between 1 and 62 episodes. Recurrent episodes of CP were more common than AP. In individuals with five or more recurrent episodes, 91% had alcohol as the aetiology for their pancreatitis.

Prevalence of Acute and Chronic Pancreatitis

The prevalence of AP was 171 per 100 000 in 2009 and 203 per 100 000 persons in 2018. The prevalence of CP was 206 per 100 000 in 2009 and 114 per 100 000 persons in 2018. When stratified by ethnicity AP in Aboriginal people was 385 per 100 000 in 2009 and 523 per 100 000 persons in 2018. In non-Aboriginal people, AP was 61 per 100 000 in 2009 and 52 per 100 000 persons in 2018. CP prevalence in Aboriginal people was 511 per 100 000 in 2009 and 273 per 100 000 persons in 2018. In non-Aboriginal people prevalence of CP was 13 per 100 000 in 2009 and 10 per 100 000 persons in 2018 (Figure 2).

Aetiology of Acute and Chronic Pancreatitis

Alcohol was the most common aetiology ascribed to AP and CP, and was particularly notable in CP. When stratified by ethnicity, alcohol was the most frequent aetiology in Aboriginal

people and biliary disease was more common in non-Aboriginal people. Of note, the aetiology was undetermined in a quarter of the non-Aboriginal cohort (Figure 3).

Diabetes

Half of the total cohort had a diagnosis of diabetes, including 61% of Aboriginal people and 22% of non-Aboriginal people. Diabetes was more prevalent in people with CP at 73% compared to AP at 44%. Diabetes was present in 31% of all individuals before their first episode of pancreatitis. This was T2D in all except one case (99%).

Diabetes After Pancreatitis

Of the 438 people with no medical record of diabetes before their first episode of pancreatitis, 125 (29%) were detected to have a diagnosis of diabetes after pancreatitis. Diabetes-associated antibodies were performed in 22 of the 125 cases and 20 were negative, meeting the case definition of PPDM. In 20 of the 125 cases, a faecal elastase test was performed, and all results were < 200 ug/g indicating pancreatic exocrine insufficiency (PEI). Only 8 of the 20 PPDM cases underwent faecal elastase testing, and all were < 200 ug/g suggesting PEI. Results of pancreatic imaging in the PPDM group demonstrated changes consistent with CP such as calcifications and duct dilatation in 45% and changes consistent with severe AP such as necrosis in 25%. The remaining imaging demonstrated changes of AP or they were normal. See Table 3 for testing rates and comparisons between diabetes diagnosed before and after pancreatitis.

DISCUSSION

This study confirms the previously reported high prevalence of AP hospitalisations in Central Australia and has provided the first estimate of prevalence of CP hospitalisations in this population. The AP prevalence rates are consistent with the prevalence estimates of between 120 and 275 episodes per 100 000 persons previously reported for this region.[1,2] This study provides the first prevalence estimates of CP in this region which were 206 per 100 000 persons in 2009, and 114 per 100 000 persons in 2018. When stratified by ethnicity the annual prevalence of AP and CP were consistently higher in Aboriginal people than non-Aboriginal people over the 10 years. The primary aetiology for both AP and CP was alcohol. Nearly one-third of those with no diabetes prior to pancreatitis were diagnosed after pancreatitis and a small percentage of the post-pancreatitis diabetes group had antibody testing fulfilling criteria for PPDM.

Recent data from Europe described the incidence of AP between 4.6 and 100 per 100 000[3] and regional differences of AP have been noted with the highest incidence in the American region at 58 and the Western Pacific at 44 per 100 000.[4] A Far North Queensland study reported an AP admission rate of 84 per 100 000. In that series, 40% of cases were documented in Aboriginal or Torres Strait Islander people pointing to an over-representation of this group who account for only 15.5% of the regional population.[26]

Global estimates of CP prevalence range from 10 to 52 per 100 000 persons.[27] The prevalence of CP in non-Aboriginal people in this study was broadly consistent with this at between 4 and 39 per 100 000 persons. The prevalence of CP admissions in Aboriginal people was around ten times that of non-Aboriginal people and four times higher than the highest global estimates. Half of this prevalence was related to recurrent episodes. Studies of AP and

CP prevalence demonstrate great regional and ethnic variation, which is also observed, even more starkly, in this study when comparing rates between Aboriginal and non-Aboriginal people in the same geographical region.

The major aetiologies of AP were consistent with other studies that demonstrate, to varying degrees, that alcohol misuse and biliary disease are the two primary causes of AP.[3] A study from the multicultural and socioeconomically disadvantaged population of Western Sydney found an overall biliary to alcohol ratio of 2:1, except for a sub-group of younger men born in Australia in whom alcohol dominated as the aetiology.[28] Consistent with the previous two Central Australian studies of AP, alcohol was the major aetiology in both AP and CP.

The rates of AP in Central Australia from 2009 to 2018 do not appear to reflect the impact of alcohol harm minimising legislation that has been enacted in this time as has been seen in Emergency Department presentations in 2013 and Intensive Care Unit admissions in 2018.[29] A downward trend for CP in both Aboriginal and non-Aboriginal people is noted from 2016-2018. The significance of this is not clear. It has been estimated that approximately 18% of persons will develop CP at 3 years after a sentinel episode of AP[30] so there is an expected time lag between alcohol policy change and the development of CP. A large systematic review and meta-analysis suggested a linear relationship between alcohol intake and the risk of CP in both sexes.[31] Despite this, only a small minority of heavy drinkers develop CP.[32] More recent studies suggest that alcohol-related CP is a more complex and nuanced syndrome, consisting of multiple interacting genetic and environmental factors including varying levels of alcohol intake.[33]

Definitions around diabetes secondary to pancreatic disease, including pancreatitis, are currently in flux. This study is reporting PPDM as antibody negative diabetes occurring at least 3

months after pancreatitis. Most individuals with diabetes diagnosed after pancreatitis in this study had no testing for diabetes-associated antibodies or exocrine insufficiency, meaning the actual rate of PPDM and PPDM with PEI in this population is not known. The implications of this under testing include delay in appropriate diabetes care, poor nutritional outcomes in those with untreated exocrine insufficiency and inadequate screening for secondary complications such as osteoporosis.[34]

An important finding in this study was the practise gap regarding the appropriate diagnosis of pancreatitis, its types and aetiologies and diagnosis and management of post-pancreatitis diabetes and pancreatic exocrine insufficiency. A consensus statement from 2012 recommended that endocrine and exocrine function should be assessed annually in those with CP[16] and given current evidence it would be reasonable to apply this recommendation to individuals after AP thus allowing for management based on individual endocrine and/or exocrine deficits. Health professionals in this region would benefit from further education and the development of local guidelines to better diagnose and manage PPDM and PEI in this remote setting.

Strengths of this study include the first prevalence estimate of CP in Central Australia. Case ascertainment of pancreatitis in this study was rigorous. The majority of the 544 excluded episodes were given a diagnosis of 'mild pancreatitis' on their discharge summary. Despite this, these episodes did not fit the international consensus diagnostic criteria.[20] Stratification by ethnicity allowed more precise epidemiological assessments that could be used to target future risk reduction strategies and therapeutic services.

The Central Australian region is sparsely populated so it can be expected that even small movements of people in or out of the region could influence prevalence rates. A potential for bias is

also acknowledged in the aetiology of pancreatitis based on a prevailing stereotype of Aboriginal people being heavy drinkers of alcohol. A further limitation of the study is that it is not known whether individuals were being deliberately screened for diabetes after pancreatitis, whether screening results were due to primary health care facilitated annual review for Aboriginal adults or whether they represented opportunistic screening outside of primary care. There is also a potential for underestimation of diabetes diagnoses given records of local General Practices and Aboriginal Community Controlled Health Services were not accessed.

CONCLUSION

This study describes a medically vulnerable group of people in Central Australia with high rates of pancreatitis and diabetes, with Aboriginal people carrying most of this burden. The high prevalence of acute, recurrent acute and chronic pancreatitis in Central Australia is associated with alcohol excess. Public health initiatives to reduce alcohol consumption have had some effect on alcohol-related harm in the region[7] but ongoing population based interventions are required to reduce this further. The very high prevalence rates of pancreatitis in this study portend higher rates of PPDM than were identified due to the underuse of diagnostic tests. In this epidemic of both T2D and pancreatitis, PPDM and PPDM with PEI, need to be recognised as separate entities to T2D[34] that require appropriate diagnosis and management.

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Figure 1: STROBE diagram

Figure 2: Prevalence of episodes of Acute and Chronic Pancreatitis by ethnicity 2009-2018 per 100 000 persons.

Denominator based on census data for resident population aged ≥15 years living in
Central Australia Health Service catchment area.
Population 2009-2013 based on 2011 census data - Aboriginal 14 278, Non-Aboriginal 22 615. Total 36 893.
Population 2014-2018 based on 2016 census data - Aboriginal 13 924. Non-Aboriginal 21 135. Total 35 059.

Figure 3: Aetiology of Pancreatitis by Type and Ethnicity

The four most common causes of 'Other' aetiology were Hypertriglyceridaemia (n=6),
Medications (n=6; DPP-4i = 3), Hypoperfusion/ shock (n=6) and
Oncologic including Pancreatic Cancer (n=5).

Table 1: Key Clinical Definitions used in the Study

	Definition	**Comment**
Acute Pancreatitis	Two of three: Upper abdominal pain, Elevation of Lipase or Amylase > 3 x ULN, Radiological features consistent with AP.	Revised Atlanta Criteria.[1] Rule out other causes of upper abdominal pain.
Recurrent Acute Pancreatitis	More than one episode of AP > 1 month apart.	
Chronic Pancreatitis	Definite Case: Either 1. Definitive imaging of Cambridge Grade 4 (pancreatic calcifications, gland atrophy or significant duct abnormalities) or 2. Consistent imaging with PEI +/- Pancreatic enzyme elevation > 3 x ULN.	Cambridge Classification adapted for Computerised Tomography.[2]
Post-Pancreatitis Diabetes Mellitus	A new diabetes diagnosis at least 3 months after the first episode of pancreatitis and negative for diabetes-associated antibodies.	As defined by Petrov & Basina 2021.[3]
Pancreatic Exocrine Insufficiency	Faecal Elastase test < 200 ug/g.[4]	

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Table 2: Patient Characteristics

	Total (n=638)	Aboriginal (n=467)	Non-Aboriginal (n=171)	p value
% of total cohort	100	73	27	
Episodes (n)	1563	1323	240	< 0.001
Female (%)	308 (48)	230 (49)	78 (46)	0.42
Median age first pancreatitis (IQR)	44 (±23)	42 (± 23)	49 (± 16.7)	< 0.001
Pancreatitis Type & Recurrence				
Acute Pancreatitis n (%)	495 (78)	342 (73)	153 (89)	< 0.001
Chronic Pancreatitis n (%)	143 (22)	125 (27)	18 (11)	< 0.001
Recurrent AP episodes (n)	382	340	42	<0.001
Recurrent CP episodes (n)	543	516	27	0.070
Aetiology of Pancreatitis				
Alcohol n (%)	353 (55)	310 (66)	43 (25)	< 0.001
Biliary n (%)	163 (25)	99 (21)	64 (37)	
Other n (%)	45 (7)	26 (6)	19 (11)	
Unknown n (%)	77 (12)	32 (7)	45 (26)	
Diabetes				
Total DM diagnosis n (%)	325/638 (51)	287/467 (61)	38/171 (22)	< 0.001
DM Before Pancreatitis n (%)	200/638 (31)	179/467 (38)	21/171 (12)	< 0.001
Diabetes After Pancreatitis				
At risk for DM After Pancreatitis n (%)	438/638 (69)	290/467 (62)	150/171 (88)	< 0.001
Diabetes After Pancreatitis n (%)	125/438 (29)	108/290 (38) †	17/150 (11)	< 0.001
Diabetes after Pancreatitis with PEI n (%)	20/438 (4.6)	16/290 (5.5)	4/150 (2.6)	
PPDM n (%) ‡	20 (4.5)	16 (5.5)	4 (2.6)	
PPDM with PEI n	8	7	1	
PPDM - imaging c/w CP n (%)§	9 (45)	9	0	

PPDM - imaging c/w SAP n (%)§	5 (25)	1	4

AP Acute Pancreatitis; **CP** Chronic Pancreatitis; **DM** Diabetes Mellitus; FE-1: Faecal-Elastase-1; **IQR** Inter-quartile Range; **PPDM** Post-Pancreatitis Diabetes Mellitus; **PEI** Pancreatic Exocrine Insufficiency; **SAP** Severe AP

† 9 Aboriginal people had no testing for diabetes prior to pancreatitis. Included in After Pancreatitis Diabetes group.

‡ Diabetes-associated antibody negative.

§ Imaging consistent with CP - calcification, duct dilatation or significant atrophy. Imaging with necrosis consistent with severe AP.

Table 3: Select Investigation Results in Diabetes diagnosed before and after first episode of pancreatitis.

	Total n=325	DM Before n=200	DM After n=125
Faecal Elastase-1(ug/g) §			
Normal (>200) n	3	3	
Moderately low (100-200) n	1	1	
Severely Low (< 100) n	9	2	7
Very Severely Low (< 15) n	14	1	13
C-Peptide (nmol/L)‡			
≤ 0.2 n	22	8	14*
>0.2 n	48	9	39
GAD Antibody¶			
Negative	26	6	20
Positive	3†	1*	2
Pancreatitis Aetiology	325	200 (62)	125 (38)
Alcohol n (%)	195	95 (48)	100 (80)
Biliary n (%)	82	67 (34)	15 (12)
Other n (%)	25	20 (10)	5 (4)
Unknown n (%)	23	18 (9)	5 (4)

DM = Diabetes Mellitus; GAD = Glutamic Acid Decarboxylase

* One GAD positive - autoimmune diabetes

† Two individuals with Chronic Pancreatitis

§ Faecal-Elastase Testing measured in n=23 Aboriginal people & n=4 non-Aboriginal people

‡ C-peptide measured in n= 57 Aboriginal people & n=16 non-Aboriginal people

¶ GADA measured in n=24 Aboriginal people and n=5 non-Aboriginal people