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ORIGINAL ARTICLE

Pancreoprivic diabetes: A clinico-etiological perspective from a single center in Andhra Pradesh, India

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Abstract

Background Pancreoprivic diabetes is a brittle form of diabetes arising from a pancreatic disease. It is often associated with glycemic variability, exocrine insufficiency and risk of hypoglycemia. Studies focusing on its profile are scarce in India. This study aims to understand the clinico-etiological profile of pancreoprivic diabetes.

Methods Eighty consecutive patients with pancreoprivic diabetes were evaluated in this cross-sectional, observational study for pancreatic exocrine and endocrine insufficiency, and complications of diabetes.

Results The mean age of the study group was 38.68 years and the mean HbA1c and stimulated C-peptide levels were 10.3% and 0.96 ng/ml, respectively. About 57.5% of the patients had BMI less than 18.5 kg/m^2. Alcoholic pancreatic diabetes (APD) (70%, $n=56$) and fibro-calculus pancreatic diabetes (FCPD) (13.75%, $n=11$) were the commonest. Primary hyperparathyroidism ($n=5$), familial hypertriglyceridemia ($n=3$), hemochromatosis, pancreas divisum, autoimmune pancreatitis, acute pancreatitis and post pancreatectomy ($n=1$, each) accounted for the remaining (16.25%, $n=13$). Pancreatic calcifications, neuropathy, nephropathy, and retinopathy were seen in 69.6%, 52.5%, 8%, and 5% of patients respectively.

Conclusion Pancreoprivic diabetes has a distinct pancreatic pathology, poor glycemic status, and low BMI. A high prevalence of pancreatic calcifications and neuropathy is seen. Besides APD, there are many other rare metabolic and anatomical etiologies.

Keywords Pancreoprivic diabetes · High index of suspicion · Low BMI · Poor insulin reserve · Insulin and enzyme replacement

Introduction

Diabetes mellitus (DM), due to disease of the exocrine pancreas, is referred to as pancreoprivic diabetes in the American Diabetes Association (ADA) classification of diabetes mellitus, 2021 [1]. This form of diabetes due to pancreatic etiology, especially chronic pancreatitis is sometimes insidious in onset and often mistakenly diagnosed as type 2 diabetes (T2DM) until the typical presentation manifests [2]. The diagnosis and management of pancreoprivic diabetes have important clinical implications both from the endocrine and exocrine perspectives. The approach to the management of these patients demands appropriate early pickup, and effective replacement of both insulin and pancreatic enzymes during the treatment and follow-up [3].

The estimated prevalence of pancreatic diabetes is 5 to 10% among diabetes patients as reported from various studies in the western population [3]. In India, the exact prevalence of pancreoprivic diabetes is not known, whereas the

Highlights
- Pancreoprivic diabetes has a distinct picture of pancreatic pathology, a poor islet cell reserve and low BMI.
- Alcoholic pancreatic diabetes is the most common form of pancreoprivic diabetes.
- Poor glycemic status and a high prevalence of neuropathy are seen.
- Optimal insulin and pancreatic enzyme replacement hold the key to management.

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prevalence of fibro-calculus pancreatic diabetes (FCPD) and alcoholic pancreatic diabetes (APD) was reported as 0.2% and 0.1%, respectively by Papita et al. [4]. The most common cause of pancreoprivic diabetes is chronic pancreatitis as reported in the Japanese epidemiological study [5]. The presentation of diabetes in these cases is quite late in the course of the disease, and often the patients do not recognize any link between the early symptoms of chronic pancreatitis like recurrent abdominal pain and malabsorption, and the seemingly unrelated diabetes that presents much later [6]. Furthermore, even among the patients with chronic pancreatitis depending on the underlying cause, a lot of heterogeneity is seen with respect to the proportion of them who actually develop diabetes as well as the age of onset [5, 7]. Chronic pancreatic inflammation results in irreversible fibrosis of islet cells to a variable extent, which may be the common underlying mechanism involved in the eventual progression to diabetes. In contrast to the classical forms of DM, the peculiar predicament of pancreoprivic diabetes is the additional involvement of alpha cells and pancreatic polypeptide (PP) secreting cells of the islets which influence the course of the disease and pose considerable therapeutic challenges.[7] Additionally combined islet cell dysfunction and exocrine pancreatic insufficiency in pancreoprivic diabetes limit the use of oral antidiabetic drugs (OADs) in the management of disease, and insulin replacement is the natural treatment of choice in these patients [8]. Balakrishnan. V. et al., in their prospective Indian survey on chronic pancreatitis, reported that idiopathic pancreatitis was the most common form of chronic pancreatitis, followed by alcoholic pancreatitis [9], but there is a dearth of literature regarding the prevalence, etiological, clinical, and complication profile of pancreoprivic diabetes, especially in the Indian context. The present study was designed with the objective to understand the clinical and etiological profile of pancreoprivic diabetes in the Indian population.

Materials and methods

This was a single-center, prospective, cross-sectional, observational study conducted between April 2019 to October 2021 at the Department of Endocrinology of a medical college hospital, in southern India. All the consecutive patients with pancreoprivic diabetes, presenting to the outpatient or inpatient services, and willing to give signed informed consent for study participation, were enrolled in this study.

Patients with pancreoprivic diabetes patients in our study were included with those with diabetes and the following criteria:

(1) a. h/o chronic, recurrent, or acute pancreatitis with or without associated features of exocrine pancreatic insufficiency.

b. h/o pancreatectomy or anatomic anomalies like pancreatic divisum.

(2) Imaging evidence of pancreatic pathology (by CT, MRI, or ultrasound) such as calcification, atrophy, etc.

(3) Presence of insulin secretory deficits (low stimulated C-peptide levels) [4].

And among those patients with an absence of classical clinical or imaging features of pancreatic pathology, documented absence of autoantibodies (GAD antibodies < 5 units/ml) suggestive of T1DM, and presence of low fecal elastase (< 200 mcg/g), pancreoprivic diabetes was diagnosed. Patients with all the above characteristics are diagnosed with pancreoprivic diabetes and included in the study.

Because of high prevalence of chronic alcohol intake in our study group, and the high financial cost of GAD antibodies and fecal elastase estimation in the Indian context, we could not strictly follow the major and minor criteria for diagnosing type 3 C DM (pancreoprivic diabetes) as proposed by Ewald et al. [7]. We have analyzed GAD antibodies and fecal elastase only in those patients with absent clinical exocrine insufficiency and altered pancreatic morphology on imaging.

Patients with type 1 diabetes (T1DM), diabetic ketoacidosis (DKA), T2DM patients on OADS including those on dipeptidyl peptidase-4 (DPP-4), and glucagon-like peptide-1 (GLP-1), patients on antiretroviral therapy, on medications implicated in the causation of pancreatitis such as steroids, anticonvulsants like sodium valproate, and pregnant women with diabetes were excluded.

Detailed history with a focus on clinical features at the time of presentation, presence of abdominal pain and steatorrhea, weight loss, and duration of diabetes were recorded from all patients. Complete examination including anthropometry and evaluation of complications was done. The patients were categorized into different BMI categories according to the Asian cut-off given by the world health organization (WHO). Blood samples were obtained from all the patients for conducting complete blood count, renal function tests, liver function tests, fasting lipid profile, serum calcium, phosphorus, serum amylase, serum lipase, fasting plasma glucose (FPG), 2-h postprandial glucose (PPG), hemoglobin A1c (HbA1c), and stimulated C-peptide.

The disease of the exocrine pancreas was assessed by clinical history, abdomen x-ray, and USG/CT abdomen. After optimizing glycemic control, C-peptide levels after a mixed meal tolerance test was done in all patients. After 90 min, the blood sample was collected and serum was separated after cold centrifugation at 2 °C for 10 min at 2000 rpm and stored at − 70 °C.

HbA1c levels were measured using the ion-exchange high-performance liquid chromatography technique (Bio-Rad Laboratories, Hercules, CA, USA) with an intra- and inter-assay coefficient of variation of 0.4 and 1.6%,

respectively. The stimulated C-peptide level was determined by the ELISA method (Calbiotech C-peptide Elisa kit).

Statistical analysis

Qualitative and quantitative variables are presented using descriptive statistics. Quantitative variables were evaluated using a paired *t*-test at a 5% level of significance and the corresponding *p*-value is presented. While medians and IQR were compared using the non-parametric Mann–Whitney *U* test. p-value < 0.05 was considered significant. Data were analyzed using SPSS® statistics software, version 21.0 (IBM Corp., Armonk, NY, USA).

Table 1 Patient characteristics at baseline ($N = 80$)

Parameter	Overall ($N = 80$)
Sex, *n* (%)	
Male	66 (82.5%)
Females	14 (17.5%)
Age (years), mean ± SD	38.68 ± 6.96
Etiology of pancreoprivic diabetes,	
Acute pancreatitis	01 (1.3%)
Autoimmune pancreatitis	01 (1.3%)
Hemochromatosis	01 (1.3%)
Post pancreatectomy	01 (1.3%)
Pancreas divisum	01 (1.3%)
Hypertriglyceridemia	03 (3.8%)
Primary hyperparathyroidism	05 (6.3%)
Fibro calcific pancreatic diabetes (FCPD)	11 (13.8%)
Alcoholic pancreatic diabetes (APD)	56 (70.0%)

Results

A total of 80 patients (male: female—66:14), with a mean (SD) age of 38.68 (± 6.96) years were enrolled in the study. The demographic and baseline characteristics and the biochemical profile of patients are summarized in Table 1.

The mean age of the study population was 38.68 years. A majority of the study participants ($n = 56$, 70%) had APD and all of them were males. FCPD was the second most common etiology ($n = 11$, 13.75%). The rest of the thirteen patients included various etiologies as presented in Table 1. The mean BMI (SD) was 18.25 (2.3) kg/m^2 with 46 (57.5%) patients having low BMI and 28 (35%) patients with normal BMI and only six (6) (6.25%) patients were overweight. About 77 patients (96%) recalled a history of weight loss or osmotic symptoms and 49 (61%) patients recalled at least one episode of steatorrhea as presented in Fig. 1. A higher proportion of APD patients (71%) had steatorrhea compared to FCPD (54%) though the difference was not statistically significant ($p = 0.234$). The mean age of onset of diabetes was significantly higher ($p = 0.002$) in APD patients (37 years) compared to FCPD patients (24.5 years). The mean duration of diabetes was 3.34 years in the entire group and was significantly shorter in APD compared to FCPD patients (3 years vs. 5.15 years; $p = 0.032$) (Table 2).

Glycemic control was poor in our study participants with a mean (SD) FPG of 195 (61) mg/dL, 2-h PPG of 316.5 (76) mg/dL, and HbA1c of 10.05 (2.19)%. The mean (SD) stimulated C-peptide levels were 0.96 (0.51) ng/mL in the overall population and were comparable ($p = 0.332$) between APD (1.1 [0.54]) and FCPD patients (0.83 [0.42]). The mean (SD)

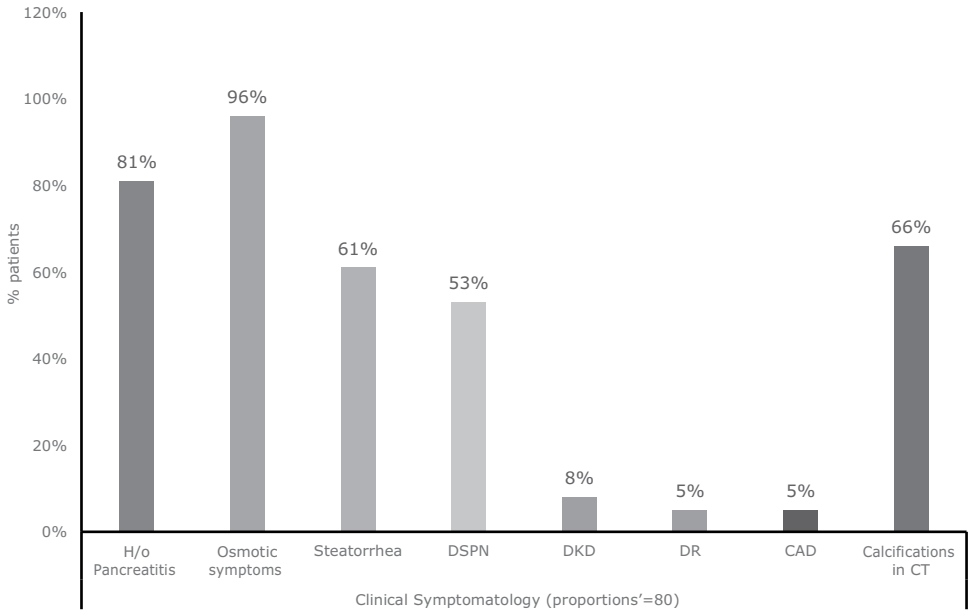

Fig. 1 Clinical symptomatology (proportions)

Table 2 Clinical and laboratory characteristics of the study group

	$N=80$
Duration of DM (years), mean ± SD	3.34 ± 2.64
Duration of alcohol intake (years), mean ± SD ($n=43$)	10.59 ± 7.3
BMI (kg/m^2), mean ± SD	18.11 ± 1.82
FPG (mg/dl), mean ± SD	210.3 ± 51.84
2-h PPG (mg/dl), mean ± SD	327.25 ± 57.93
HBA1c (%), mean ± SD	10.3 ± 1.49
S. lipase (IU/L), mean ± SD	80.49 ± 51.2
S. amylase (IU/L), mean ± SD	115.97 ± 62.73
S. calcium (mg/dl), mean ± SD	9.14 ± 0.74
S. phosphate (mg/dl), mean ± SD	3.46 ± 0.52
S. creatinine (mg/dl), mean ± SD	0.98 ± 0.4
Total bilirubin (mg/dl), mean ± SD	1.02 ± 0.46
SGPT (IU/L), mean ± SD	37.34 ± 22.55
SGOT (IU/L), mean ± SD	39.26 ± 19.42
ALP (IU/L), mean ± SD	161.4 ± 90.58
C-peptide (ng/ml), mean ± SD	0.96 ± 0.51
GAD antibodies normal range < 5units/ml	< 5 unit ns/ml ***N* = 3**
Fecal elastase normal range > 200 mcg/g	103mcg/g ***N* = 3**

ALP, alkaline phosphatase; *BMI*, body mass index; *FPG*, fasting plasma glucose; *2 h PPG*, 2 h postprandial glucose; *SGOT*, serum glutamate–oxaloacetate transaminase; *SGPT*, serum glutamate-pyruvate transaminase

C-peptide levels were lower in smokers compared to non-smokers (0.86 [0.49] vs. 1.01 [0.52] ng/ml) but were comparable ($p=0.562$) between the groups. Study data did not show a significant correlation between stimulated C-peptide levels and HbA1c. Anti-GAD antibodies were negative in all the participants.

Serum amylase and lipase values were higher in APD compared to FCPD after excluding the outliers but missed statistical significance probably due to the low number of FCPD patients in our study. Analysis of the chronic complications of diabetes in our study revealed that 42 (52.5%) patients had distal symmetric peripheral neuropathy (DSPN), 6 (8%) patients had diabetic kidney disease (DKD), and 4 (5%) patients had diabetic retinopathy (DR). Coronary artery disease (CAD) was present in four (5%) patients, out of these three had APD, one was a current smoker, and one patient had hyperparathyroidism. About 85% of the patients with neuropathy had APD. No other macrovascular complication was noted among our study patients.

Hypocalcemia (serum calcium < 8.5 mg/dl) was noted in 11 (15%) patients, with normocalcemia (serum calcium 8.5–10.5 mg/dl) seen in 55 (78%) patients and five (5) (6.2%) patients with primary hyperparathyroidism had hypercalcemia. Radiological evaluation of the study group showed that the CT scan was more sensitive than the abdominal X-ray in detecting calcifications. In APD patients, pancreatic calcifications were noted in 39 (69.6%) patients, while in FCPD it was noted in 11 (100%) patients. The rest of the patients had atrophic pancreas, except one patient with features of acute pancreatitis. However, only 10 (12%) patients had pancreatic calcifications noted in the abdomen x-ray of whom six patients had APD and four patients had FCPD.

Analyzing the overall patient profile in the study, out of the 80 patients included in our study, 70% ($n=56$) of the group presented with diabetes, steatorrhea, and pancreatic calcification and 23.75% ($n=19$) had atrophic pancreas on CT scan abdomen, 2.5% ($n=2$) had pancreatic divisum and pancreatectomy. In the entire cohort, only 3.75%, i.e., 3 patients had normal BMI, imaging, and absent GAD antibodies no steatorrhea or weight loss but low fecal elastase levels on estimation (103 mcg/g (normal range > 200 mcg/g) documenting exocrine pancreatic insufficiency (Table 3).

Discussion

Diabetes mellitus is an increasingly prevalent metabolic disorder of which T2DM is the commonest form. It largely has an asymptomatic presentation with a younger age of onset particularly in India, sometimes presenting with chronic complications at diagnosis. Other specific forms of diabetes may be misdiagnosed as T2DM until the classic expression of the underlying condition is picked up [10]. In the recent ADA classification 2021, diabetes due to disease of the exocrine pancreas has been referred to as pancreoprivic diabetes [1]. There is a dearth of information regarding pancreoprivic diabetes, especially in India. Delay in its diagnosis and the consequent inadequate management bears a significant burden on the health care system [6]. In this study, we have explored the spectrum of etiologies and attempted

Table 3 Patient characteristics

	$N=80$
Patients presenting with diabetes, steatorrhea and pancreatic calcification	56 (70%)
Patients presenting with diabetes, steatorrhea and atrophic pancreas	19 (23.75%)
Patients presenting with pancreatectomy and pancreas divisum	2 (2.5%)
Patients presenting with normal BMI, diabetes, absent GAD antibodies, and documented low fecal elastase suggesting exocrine pancreatic insufficiency	3 (3.75%)

to understand the clinical profile as well as the long-term complications of this form of diabetes.

Our study included 80 consecutive patients with pancreoprivic diabetes presenting to an endocrinology facility in a teaching hospital in Andhra Pradesh, India. Most of the patients ($n=56$, 70%) had APD (Table 1). Notably, all of them were males, reflecting the local socio-cultural factors involved in alcoholism but none had features of chronic liver disease. Our findings concur well with the national wide survey of pancreatic diabetes in Japan, by Ito et al. who found APD to be the predominant etiology (5). FCPD is the second most common subgroup ($n=11$, 13.75%) in our study. However, Chari et al. in a comparative study of the clinical profile of chronic pancreatitis done almost 3 decades ago in Chennai reported tropical calcific pancreatitis (TCP) or FCPD as the most common cause of pancreatic diabetes.10 ([12]) This interesting shift in the etiologic spectrum in pancreoprivic diabetes seen in our study probably reflects the increased prevalence of habitual indulgence in alcoholism in the population. The age of onset of diabetes in APD was almost a decade later compared to FCPD in our study similar to that reported by Chari et al. However, the India nationwide survey reported that idiopathic pancreatitis was the most common form of chronic pancreattis, followed by alcoholic pancreatitis and tropical chronic pancreatitis is being seen less common [9].

The mean duration of alcohol consumption was 15.12 years among those with APD and the features of pancreatitis preceded the onset of diabetes by 2.7 years. In the FCPD group, on the other hand, the patients recalled the symptoms of pancreatitis 3.75 years before the onset of diabetes. The onset of dysglycaemia may be explained by five major functional changes viz., insulin and glucagon deficiency, reduced incretin effect, insulin resistance, and the genetic association with the disease [7, 11].

The mean duration of diabetes at enrolment as elicited from the patient's recall of the clinical history in our study was 2.7 years. In almost all of them, the onset was heralded by osmotic symptoms and weight loss consistent with severe insulin deficiency. The features of pancreatitis were present in 81% of our patients before the onset of diabetes and only 59% reported an episode of steatorrhea, compared to 25% as observed by Chari et al. [12].

About 57.5% of our patients had low BMI reflecting the poor nutritional status due to exocrine insufficiency, chronic alcoholism, and uncontrolled diabetes. The low BMI, a distinctive anthropometric feature of pancreoprivic diabetes reported in a few Indian studies, contrasts with the predominantly overweight phenotype seen in western literature [13, 14].

The mean (SD) HbA1c was 10.05 (2.19%) suggesting poor glycemic status and the stimulated mean (SD) C-peptide level (0.96 [0.51] ng/ml) was low in the entire group indicating poor islet cell reserve. It was lower in FCPD than APD though not statistically significant. Anne et al., in their comparative study of FCPD patients with type 1 and type 2 diabetes, observed poorer glycemic control in FCPD, with a mean stimulated C-peptide level of 1.53 ± 0.99 ng/ml [15, 16].

In another study done by Stoian et al. on pancreoprivic diabetes, the mean stimulated C-peptide level was 0.7 ng/ml and the mean HbA1c was 7.9%. These observed variations in the glycemic status and islet cell reserve may be attributed to the differences in the changing etiological profile of pancreoprivic diabetes and the mean duration of diabetes [17].

The pathophysiology of chronic alcoholic pancreatitis is complex. Toxic metabolites, the upregulation of various apoptotic genes, and the direct activation of pancreatic stellate cells account for the parenchymal injury. Genetic susceptibility sensitizes the pancreas to chronic alcohol exposure and parenchymal injury. SPINK1 gene with a significant association with hereditary pancreatitis has been linked to FCPD in some study groups. Environmental factors may also play an important role in pathogenesis [18]. However, a notable staple diet in south India formerly implicated in TCP, cassava, is mostly absolved of its perceived role in causing pancreatitis.

Our study had a few rare causes of pancreoprivic diabetes (Fig. 1). Three female patients had severe hypertriglyceridemia (TG > 2000 mg/dl) with recurrent pancreatitis leading to pancreatic diabetes. Free fatty acids possibly stimulate amylase release resulting in damage to the pancreatic acinar cell [19]. These patients were on fibrates albeit with a poor response but responded to insulin treatment. Genetic analyses could not be done due to financial constraints. Primary hyperparathyroidism with concomitant hypercalcemia pancreatic calcification and pancreoprivic diabetes were seen in five patients. Isolated case reports of this form of diabetes are available [20]. A case of HFE gene mutation-negative Hemochromatosis with pancreatic diabetes is seen in our series. The patient had features of iron overload (S. ferritin > 1000 ng/ml)—hyperpigmentation, hypogonadism, liver dysfunction, and atrophic pancreas on imaging. A generalized parenchyma loss with selective beta-cell loss and sparing of alpha cells is reported in such cases [21].

One case of pancreas divisum, which is rarely associated with chronic pancreatitis and secondary diabetes is seen in our series [22]. Autoimmune pancreatitis with diabetes is seen in one case [23]. Distal symmetric peripheral neuropathy is the commonest microvascular complication seen in our study cohort. The axonal injury occurs in both diabetes and chronic alcoholism, but a demyelinating component due to thiamine deficiency is also seen in alcoholic neuropathy. The excess glucose in diabetes is specifically diverted to polyol and hexosamine pathways which subsequently lead to the accumulation of sorbitol and acetylated dinucleotides respectively [24]. These and the advanced

glycation end products formed in poorly controlled diabetes increase reactive oxygen species (ROS) production [24]. In one of our earlier studies, we have demonstrated that uncontrolled diabetes results in oxidative stress and decreased mitochondrial oxidative capacity [25]. The production of ROS is also implicated in the disruption of mitochondrial axonal trafficking underlying the distal to the proximal pattern of axonal nerve damage [24].

Barman et al. studied FCPD patients with a mean duration of diabetes of 11 ± 10 years in Chennai and reported retinopathy in 36.1% and nephropathy in 10.1% [26]. Notably, Ito et al. in their study found the prevalence of microvascular complications to be increasing according to the duration of diabetes [5]. Macrovascular complications are rare in pancreoprivic diabetes owing to the concurrent malabsorption and normal lipid levels and low BMI as is seen in our study. Coronary artery disease was present in four (5%) patients who had a history of chronic smoking. An interesting finding is the presence of hypocalcemia in a significant proportion of our patients ($n = 11$ [13.75%]) suggesting the compounding effects of concurrent malabsorption and vitamin D deficiency. A pooled prevalence of vitamin D deficiency in chronic pancreatitis patients was reported to be 65% by Hoogenboom et al. [27]. It is difficult to comment on the contribution of chronic pancreatitis to hypocalcemia due to the high prevalence of vitamin D deficiency in the general population.

All our patients with FCPD and 39 (69.6%) patients with APD had calcifications noted in the pancreas. Balakrishnan et al. and Stoian et al. noted the prevalence of pancreatic calcification to be 64.6% and 66.1% respectively [17, 18]. Though the degree of calcifications is often proportional to the severity of pancreatitis, there is a poor correlation between the degree of parenchymal changes and the exocrine insufficiency or the islet cell dysfunction [28, 29]. The mean (SD) amylase (122.28 [36.7] IU/L) and lipase (83.34 [40.35] IU/L) were higher than normal but there was no significant difference between the groups, probably due to pancreatic fibrosis and exocrine insufficiency. This reiterates the assumption that the onset of diabetes occurs quite late in the course long after the first presentations of pancreatitis [30].

Among our study cohort, nearly 95% of had pancreatic pathology on imaging (calcification and atrophy and pancreas divisum and pancreatectomy respectively, Table 3), and only 3 patients (3.75%) presented with normal BMI, diabetes, and no evidence of clinical apparent malabsorption, but had low fecal elastase levels (103 mcg/g, normal range <200 mcg/gm) indicating exocrine pancreatic insufficiency along with low C−peptide. Hence, because of the high financial costs involved, we have evaluated GAD antibodies and fecal elastase levels only in those patients where no clinical or imageological evidence of pancreatic pathology was documented.

Management of pancreoprivic diabetes patients involves early detection with a high index of suspicion and effective treatment of exocrine pancreatic insufficiency and uncontrolled diabetes. Metformin is suggested as a preliminary antidiabetic agent, and it also reduces the risk of pancreatic cancer which is otherwise increased both in the setting of chronic pancreatitis and diabetes. Most patients will eventually need insulin treatment and insulin treatment serves as an anabolic physiological replacement therapy [31], especially in the patients with low BMI phenotype and undernutrition and malabsorption. Sodium-glucose transport protein 2 (SGLT2) inhibitors are contraindicated given the catabolic state that is seen in these patients. Optimizing glycemic control in pancreoprivic diabetes involves insulin replacement in a near-physiological manner, with periodic monitoring. Incorporating self-monitoring of blood glucose (SMBG)/continuous glucose monitoring (CGM) in multiple-dose insulin treatment facilitates early pick up of asymptomatic nocturnal hypoglycemia and brittle diabetes. The addition of pancreatic enzyme replacement therapy (PERT) improves nutrient absorption and intermediary metabolism and renders the patient more resistant to fluctuations in blood glucose. However, the cost remains a concern in developing nations and cheaper alternatives are the need of the hour. Usual dosages range from 10,000 units with a snack to about 40–50,000 units with meals titrated to the quantity of fat in the meals and clinical response [32]. Parenteral vitamin replacements and medium-chain fatty acids and increased calorie intake are important. Replacement of fat-soluble vitamins (A, D, E, K) and an adequate amount of micronutrients such as calcium, magnesium, and B12 is essential. Of note, a few studies are underway to study the effects of PERT on glycemic control using CGM devices [33]. In summary, pancreoprivic diabetes is a specific clinical entity due to a variety of underlying causes of pancreatic insult, and its treatment demands team-oriented management balancing both endocrine and exocrine issues. Though our study included only 80 patients, it offers an insightful description of the various causes of pancreoprivic diabetes and focused on the pathophysiologic perspective of management of this form of diabetes.

Conclusion

Pancreoprivic diabetes often presents with low BMI, poor insulin reserve and glycemic status, and a short duration of diabetes. Alcoholic pancreatic diabetes is the most common cause and certain rare metabolic and anatomical causes can also cause this specific form of diabetes. A high index of suspicion is needed for the early pickup and effective replacement of both insulin and pancreatic enzymes holds

the key to the management of pancreoprivic diabetes. It reinforces the emergent need of tackling the menace of chronic alcoholism.

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Declarations

Ethical approval The study was conducted in conformity with the principles of the Declaration of Helsinki, International Council for Harmonization-Good Clinical Practices (ICH-GCP) guidelines, Indian Council of Medical Research, Indian GCP guidelines, and as per the approved protocol. Written informed consent was obtained from all study participants, before being examined for eligibility criteria. The study protocol and the informed consent form were reviewed and approved by the institutional ethics committee of Andhra Medical College, Visakhapatnam, Andhra Pradesh, India.

Conflict of interest The authors declare no competing interests.

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