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Comparative study on the diabetes mellitus profile in Carcinoma in Chronic Pancreatitis and Denovo Carcinoma Pancreas

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Abstract
Introduction: Carcinoma pancreas has dismal prognosis and diabetes is a risk factor. Recent-onset diabetes in which pancreatic cancer was diagnosed were early-stage, suggesting possibility for early detection. Chronic pancreatitis (CP) is an inflammatory disease with progressive impairment of exocrine and endocrine functions; 19% alcoholic CP and 56% tropical CP were diabetic. Methodology: single centre retrospective comparative study is done in Department of Surgical Gastroenterology, in pancreatico-duodenectomy cases done from 01/01/2004 to 31/12/2013 for carcinoma in CP or denovo carcinoma pancreas. Results: Diabetes was associated more with CCP-Ca than denovo Ca (70.7%vs44.6%). Recent-onset diabetes was found more in CCP-Ca than Denovo Ca (41.1% vs 16.9%; p=0.003). Mean blood sugar in CCP-Ca was 193.3±110, significantly higher than Denovo-Ca 136.2±70. Uncontrolled diabetes at presentation was significantly more in CCP-Ca (43.1%) than Denovo-Ca (18.6%). Worse diabetes in CCP-Ca could be due to the baseline endocrine defects in CP. The mean blood sugar value in CCP-Ca was higher but not significant, in cholangitis compared to no cholangitis patients (202.03±104 vs 184.5±117.03; p<0.50). Mean blood sugar in Denovo-Ca was significantly higher in cholangitis compared to no cholangitis (148.8±78.2vs =115.7±45.7; p=0.002). Long duration diabetes in CCP might have sensitised tissues, may be the reason for lesser incidence of cholangitis in CCP-Ca. Conclusion: Though the parameters related to diabetes were worse among CCP-Ca than denovo-Ca, clinical complications and infective complications like cholangitis was not significant.

Keywords: Type III diabetes, diabetes in chronic pancreatitis, diabetes in carcinoma pancreas, CCP

Introduction

Pancreatic cancer is a disease having dismal prognosis with a 5-year survival rate of less than 10%[1]. Many studies have identified type 2 diabetes as a risk factor for pancreatic cancer. It was suggested by another study that diabetes may be a consequence rather than a risk factor for pancreatic cancer[2]. However many others have reported diabetes as a clinical presentation of pancreatic cancer. It is reported that most patients with recent-onset diabetes in whom pancreatic cancer was diagnosed had early-stage cancer at diagnosis of diabetes, suggesting a possibility for managing such patients by early diagnosis and an intention to cure treatment[3].

Chronic pancreatitis (CP) is an inflammatory disease of the pancreas with progressive impairment in its exocrine and endocrine functions. The underlying cause could be increasing fibrosis of the pancreatic parenchyma and concomitant loss of islets cells; resulting in deterioration of endocrine and exocrine functions. Islet cell destruction causes loss of B-cells and A-cells, clinically results in loss of counter-regulation of hypoglycaemia, leading to 'brittle diabetes'. CP patients presenting with exocrine insufficiency is accompanied by diabetes in approximately 10% of cases, with 30% of them showing an impaired glucose tolerance. In a comparative study on different subtypes of CP, 19% of alcoholic CP and 56% tropical CP were found diabetic. Diabetes in TCP presents usually in the third decade of life and ketosis was relatively uncommon in TCP (Mohan *et al*., 1983).

In our department database on CP patients, 28.94% of benign CP and 26.7% of malignant CP were found diabetic. It was observed that the changes in the clinical profile of diabetes in CP, such as a recent onset diabetes or uncontrolled status of existing diabetes are associated with malignancy in CP. The objective of this study is to objectively compare the clinical profile of diabetes mellitus in histopathology confirmed cases of carcinoma in chronic pancreatitis with that of denovo carcinoma pancreas.

Materials and methods

This study was done as a part of the ongoing single centre retrospective comparative study in the Department of Surgical Gastroenterology, Govt. Medical College, Trivandrum, on the predictors of survival in consecutive cases of pancreatico-duodenectomy done from 01/01/2004 to 31/12/2013 for carcinoma in CP or denovo carcinoma pancreas. The sample size (n) was calculated as 40 in each group. Inclusion criteria were radiologically confirmed cases of CP with mass lesion, resected and histopathology confirmed cases as `adenocarcinoma pancreas associated with CP, included in the study as Carcinoma-in CP. Resected and confirmed cases of denovo ductal adenocarcinoma pancreas were included as Denovo Carcinoma Pancreas. Tumour stage reported as TNM stage I or II were enrolled in to this study. Exclusion criteria were CCP with dysplasia alone or other atypical cases, carcinoma pancreas with direct tumour infiltration to the adjacent structures other than duodenum or bile duct, patients with serious comorbidities and operative mortality within 30 days. The study variables included demographic details, clinical features, diabetes status, laboratory investigations, post-operative morbidity and 2 year survival. The data regarding the various parameters was compiled based on a structured proforma, after obtaining a documented consent from the individual patients.

Statistical analysis: Suitable parametric and non-parametric statistical tests were applied for comparing the clinical and

pathological parameters. Statistically significant difference was defined as the p-value <0.05. The various statistical tests were done using IBM SPSS Statistics (27.0 version).

Results

137 patients who had pancreaticoduodenal to my during this study period; among these carcinoma in CCP (CCP-Ca) was 43.1% (n=59) and de-novo carcinoma pancreas (Denovo-Ca) was 56.9% (n=78). The median age at diagnosis in CCP-Ca was 50 years and that in Denovo-Ca was 55 years, (p<0.001). The CCP-Ca group had 33 (55.9%) males and 26 (44.1%) females, Denovo-Ca group had 44 (56.4%) males and 34(43.6%) females, (p=NS).

On comparing variables regarding the diabetic status of the two groups studied the observations were as follows (Table 1) Diabetes mellitus was there in 74 (56.1%) of total patients studied (Fig.1); in 41 (70.7%) patients of CCP-Ca and in 33 (44.6%) patients of Denovo-Ca (p=0.003). Long-duration diabetes (>6 months) was there in 28.6% of CCP-Ca and 26.8% of Denovo-Ca. Recent onset diabetes (duration of DM <6 months) was observed (Fig.2) in 23 (41.1%) of CCP-Ca and 12 (16.9%) of Denovo-Ca. This was statistically significant (p=0.003).

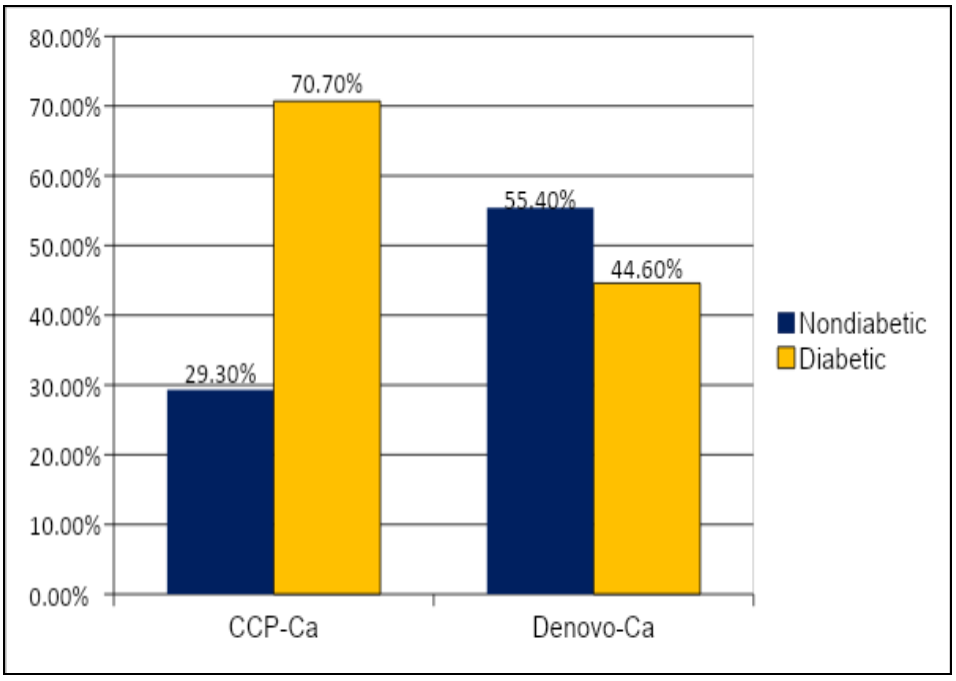

Fig 1: Diabetes in CCP-Ca and Denovo-Ca.

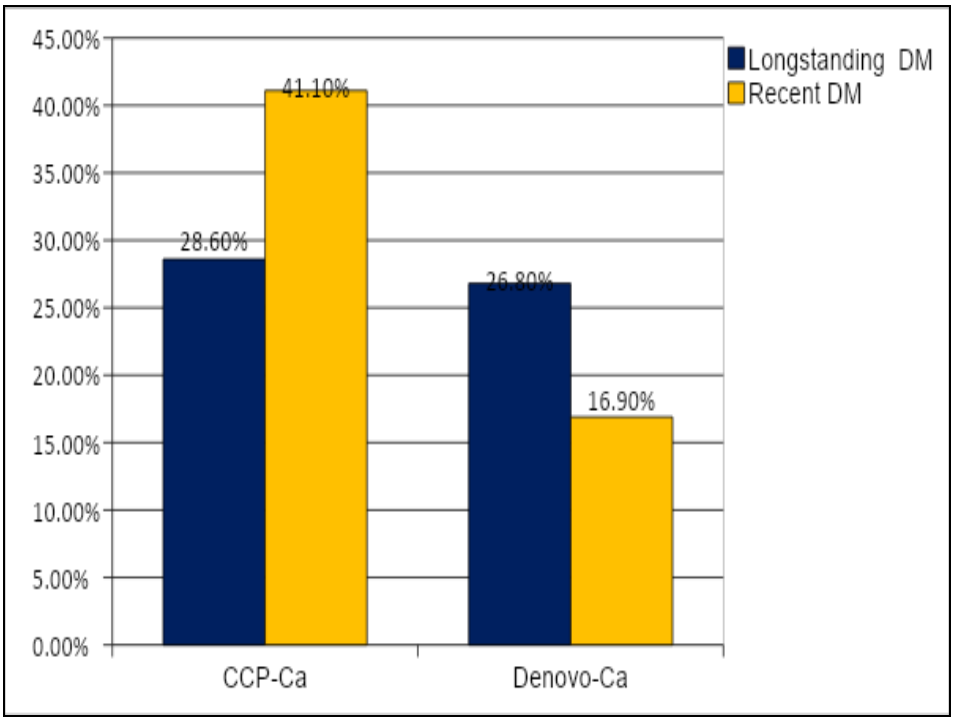

Fig 2: Nature of Diabetes in CCP-Ca and Denovo-Ca

Blood Sugar: Fasting Blood sugar values after admission in CCP-Ca ranged from 68 to 443 mg% with mean as 193.3+110 and as median 165 mg%. The fasting blood sugar level in Denovo-Ca ranged from 64 to 395 mg% with mean as 136.2+70 and as median 111mg% (Fig. 2). This difference was statistically significant (p<0.001).

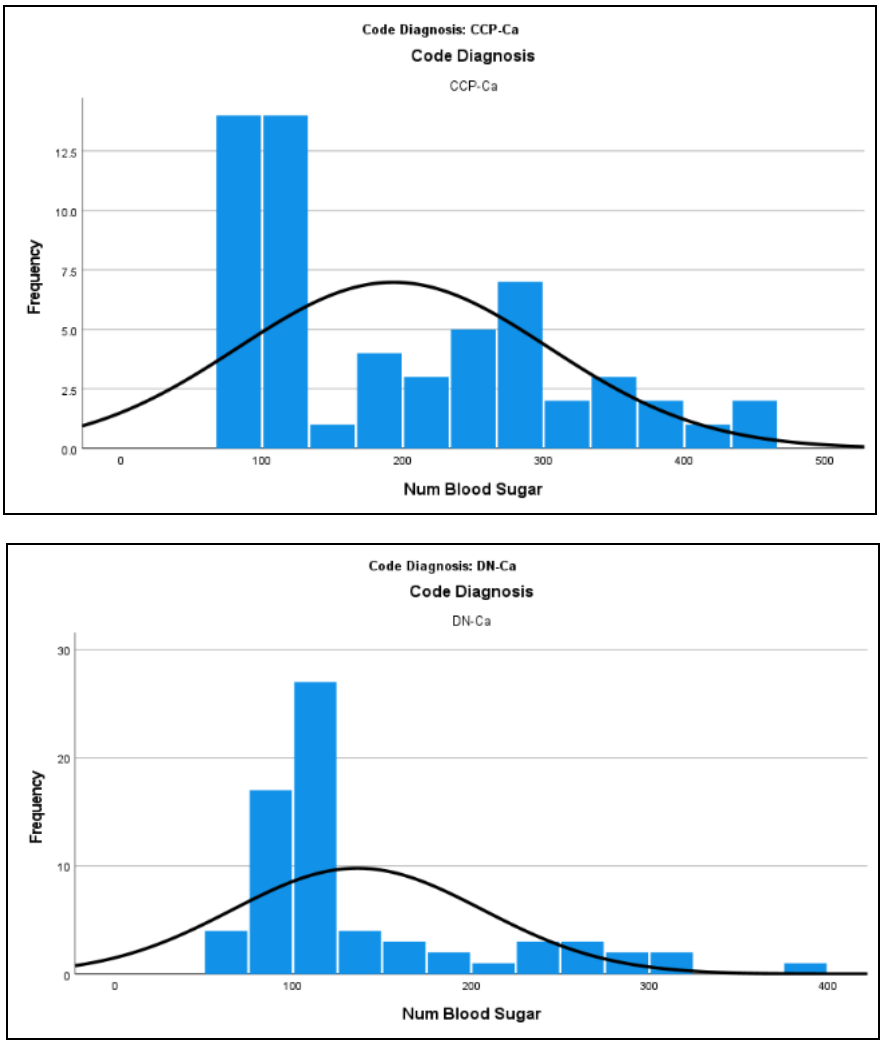

Fig 3: Blood sugar values in CCP- Ca and Denovo-Ca.

Control of Diabetes Mellitus: Diabetic status was uncontrolled (>200 mg%) at presentation in 43.1% CCP-Ca and 18.6% Denovo-Ca, which was also statistically significant (p=0.017).

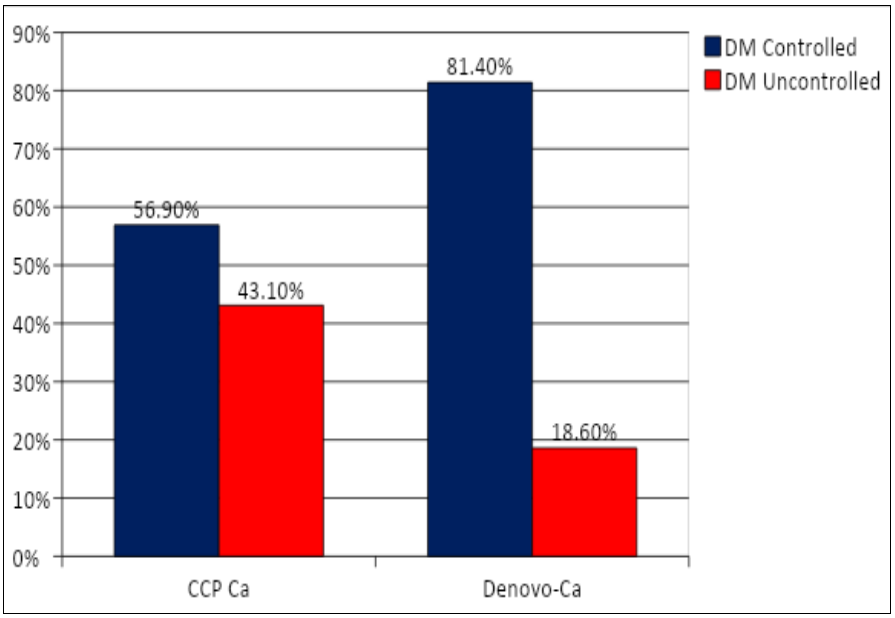

Fig 4: Diabetic status at Presentation in CCP-Ca and Denovo-Ca.

Biochemical evidence of cholangitis was there in 49.2% in CCP-Ca and in 65.2% of Denovo-Ca (p=0.071). Among those patients who had biochemical cholangitis in the Denovo-Ca group, 48.8% were diabetics and 51.2% were not diabetics (p=0.098). Among the Denovo-Ca patients with cholangitis, 91.7% had uncontrolled diabetes.

Table 1: Variables showing significant differences in diabetic status

Variable	CCP-Ca(n=59)	Denovo-Ca(n=78)	p value
Diabetes mellitus	70.7%	44.6%	p=0.003
Recent onset diabetes	41.1%	34.3%	p=0.003
Other comorbidities	28.1%	45.6%	p=0.044
Mean Blood Sugar	193.29±110.46	136.20±70.334	p<0.001
Uncontrolled diabetes	43.1%	18.6%	p=0.002
Overall post-op morbidity	12.1%	31.3%	p=0.17

Morbidity and mortality: The overall postoperative morbidity had no significant differences between CCP-Ca and Denovo-Ca. On comparing the paients who survived only for less than 24 months (2 years) after pancreatico-duodenectomy there were statistically significant differences between CCP-Ca and Denovo-Ca (Table 2). Those with diabetes were more among CPP-Ca than in Denovo-Ca (77.8% vs 53.2%; p=0.036). The mean fasting blood sugar was higher in CCP-Ca than in Denovo-Ca (186.5±9 vs 151.3±8; p=0.048). The incidence of cholangitis was more among CCP-Ca than inn Denovo-Ca and it was statistically significant (77.8% vs 44.7%; p=0.007).

Table 2: Variables showing significant differences in those survived <2 years.

Variable	CCP-Ca	Denovo-Ca	p-value
Diabetes Mellitus	77.8%	53.2%	p=0.036
Mean Blood Sugar	186.5±9	151.3±8	p=0.048
Cholangitis	77.8%	44.7%	p=0.007

Diabetes due to diseases of the exocrine pancreas is referred to as type 3c diabetes[4]. The largest study to assess prevalence among a cohort with diabetes classified 172 (9.2%) of 1868 as having type 3c diabetes[5]. Another study by Vujasinovic *et al* in 150 participants with diabetes reported a 5.4% prevalence of type 3c diabetes[6]. Various epidemiologic studies described an association between diabetes mellitus and pancreatic cancer. In a meta-analysis of 88 studies, Chari *et al*. reported the relative risk (RR) for pancreatic cancer in diabetics compared with nondiabetics as 2.08[7]. Another study from Taiwan showed the hazard ratio (HR) for the development of PDAC in CP with diabetes as 33-fold compared to the controls[8]. Sharma *et al*. reported that new-onset diabetes, compared with the general population, has a 6–8-fold increased risk for pancreatic cancer within 3 years; 60% of pancreatic cancer occurs within 12 months of diagnosis[9]. Andersen *et al* had suggested that diabetes is associated with an increased risk of PC (RR=1.94; 95% confidence interval (95% CI): 1.66–2.27). The risk of pancreatic cancer correlated inversely with the duration of diabetes, with the highest risk of PC found among patients with diabetes diagnosed within <1 year[10].

In our study, diabetes mellitus was seen associated with the majority of CCP-Ca compared to denovo Ca (70.7% vs 44.6%). Recent-onset diabetes was found more associated with CCP-Ca than with DenovoCa (41.1% vs 16.9%; p=0.003); this difference could be because of the progressive nature of the underlying CCP, in CCP-Ca patients where there are endocrine and exocrine deficiencies.

The mean blood sugar value in CCP-Ca was 193.3±110 which was significantly higher than in Denovo-Ca where it was 136.2±70. In this series, recent-onset diabetes (<6 months) was there in 41.1% of CCP-Ca and 16.9% of Denovo DACP which was a statistically significant difference. This could be due to the changes happening in CCP progressing to carcinoma. Uncontrolled diabetes (>200 mg%) at presentation was significantly more in CCP-Ca (43.1%) compared to Denovo-Ca (18.6%). The mean sugar value in CCP-Ca was higher than that of Denovo-Ca which shows worse diabetes in CCP-Ca. This could be due to the baseline endocrine defects happening in CP. Increased proportion of uncontrolled diabetes in CCP-Ca compared to Denovo-Ca is also complements this observation. The histopathological studies in CCP had demonstrated pan changes in and around the Islets of Lamgerhans in pancreatic parenchyma which can lead to global variations in the functions of islets which can involve both alpha and beta cells whereby alter the secretion of glucogon and insulin which acts to maintain the glycaemic balance.

Jain *et al*. (2017) studied cholangitis in HPB malignancy had reported that 19% of patients had cholangitis at first admission; interventions were performed in 78% (45% had percutaneous drainage and 55% had endoscopic drainage). In patients who underwent pancreaticoduodenectomy, preoperative cholangitis was seen associated with increased mortality (HR 2.67, 95% CI:1.16–6.13). Biochemical evidence of cholangitis was significantly higher among Denovo-Ca compared to CCP-Ca (65.2% vs 49.2%). Cholangitis did not show significant differences between CCP-Ca and Denovo-Ca regarding correlation with age, gender, duration of symptoms or diabetes mellitus. The mean blood sugar value in CCP-Ca was higher but not statistically significant, in cholangitis compared to no cholangitis patients (202.03±104 vs 184.5±117.03; p<0.50). However, the mean blood sugar value in Denovo-Ca was significantly higher in cholangitis compared to no cholangitis patients (148.8±78.2 vs 115.7±45.7; p=0.002). The long duration of diabetes in CCP might have sensitised tissues may be the reason for lesser incidence of cholangitis in CCP-Ca.

Conclusion

The diabetes, is it a risk factor for carcinoma or a consequence of carcinoma remains an unanswered question.

In this study though the parameters related to diabetes were found worse among CCP-Ca than in denovo-Ca, the clinical complications in the form of higher association with infective conditions like cholangitis was not observed. There should be detailed studies in this aspect focussing on the ultrastructural changes happening in CP and denovo carcinoma pancreas to explore the pathophysiology of these disease entities.

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