ORIGINAL ARTICLE

Comparative Analysis of Long-Standing and Newly Diagnosed Diabetes Mellitus in Patients with Pancreatic Ductal Adenocarcinoma: A Tunisian Multicenter Study

Analyse comparative du diabète sucré ancien et nouvellement diagnostiqué chez les patients atteints d'adénocarcinome canalaire pancréatique: Une étude multicentrique tunisienne

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Abstract

Introduction: Diabetes mellitus has emerged as a global public health issue due to its increasing prevalence and the increased risk of developing cancers. Pancreatic cancer is believed to be both a consequence of pre-existing diabetes and a potential cause of new-onset diabetes.
Aim: This study aims to compare the characteristics of patients with pancreatic ductal adenocarcinoma and newly diagnosed or long-standing diabetes mellitus.
Methods: A multicentric retrospective study was conducted over 13 years at two university hospitals in Sousse, Tunisia. Included patients had whether a newly diagnosed or a long-standing diabetes mellitus with histologically confirmed pancreatic ductal adenocarcinoma. Statistical analysis using appropriate tests was conducted.
Results: The prevalence of diabetes mellitus was 44.6% among three hundred and seven patients with pancreatic cancer. The male-to-female ratio in patients with pancreatic ductal adenocarcinoma was 2.6:1. Patients' mean age was 63.9 years, with the majority being over 50 years old. Most patients had no family history of diabetes and exhibited significant weight loss, low body mass index, and uncontrolled diabetes. The comparison between individuals with newly diagnosed diabetes and those with long-standing diabetes revealed numerous similarities, apart from significant differences in drinking patterns (p = 0.03), tumor size (p = 0.018), and smoking in the subgroup of males (p = 0.044).
Conclusion: Patients over 50 with newly diagnosed diabetes mellitus, particularly those who consume alcohol occasionally and men who are not heavy smokers, should undergo further evaluation to identify potential early-stage pancreatic ductal adenocarcinoma.

Key words: Diabetes mellitus; Pancreatic Neoplasms; Pancreatic ductal carcinoma; Smoking; Alcoholism.

Résumé

Introduction: Le diabète est devenu un problème de santé publique mondial en raison de sa prévalence croissante et du risque accru de développer des cancers. Le cancer du pancréas est une conséquence d'un diabète préexistant mais aussi une cause potentielle d'un diabète nouvellement-diagnostiqué.
Objectif: Cette étude vise à comparer les caractéristiques des patients atteints d'adénocarcinome canalaire pancréatique et de diabète ancien ou nouvellement-diagnostiqué.
Méthodes: Une étude rétrospective,multicentrique, a été menée sur 13ans dans deux hôpitaux-universitaires de Sousse,Tunisie.Les patients inclus avaient soit un diabète nouvellement-diagnostiqué, soit un diabète ancien, associé à un adénocarcinome canalaire pancréatique confirmé histologiquement.
Résultats: La prévalence du diabète était de 44,6% parmi trois-cent-sept patients atteints de cancer du pancréas.Le ratio hommes-femmes était de 2,6:1.L'âge moyen de ces patients était de 63,9ans et la majorité avait plus de 50ans.La plupart des patients n'avaient pas d'antécédents familiaux de diabète et présentaient une perte de poids significative,un faible indice de masse corporelle et un diabète mal équilibré.La comparaison entre les individus atteints de diabète nouvellement-diagnostiqué et ceux atteints de diabète ancien a révélé de nombreuses similitudes,à l'exception de l'éthylisme (p=0,03),la taille de la tumeur (p=0,018) et le tabagisme dans le sous-groupe des hommes (p=0,044) où les différences étaient significatives.
Conclusion: Les patients de plus de 50 ans nouvellement-diagnostiqué avec un diabète sucré, en particulier ceux qui consomment de l'alcool occasionnellement et les hommes qui ne sont pas de gros fumeurs, devraient subir une évaluation plus approfondie pour identifier un éventuel adénocarcinome canalaire pancréatique à un stade précoce.

Mots clés: Diabète sucré ; Tumeurs du pancréas ; Carcinome du canal pancréatique ; Tabagisme ; Ethylisme.

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What is known:
• Patients with diabetes mellitus have an increased risk of developing pancreatic cancers.
• Pancreatic cancer could cause new-onset diabetes, called type 3c diabetes.

What this article adds:
• Presence of many similar characteristics between newly diagnosed and long-standing diabetes .
• Type 3c diabetes may share the same underlying physiological mechanisms as those observed in long-standing diabetes mellitus.

Introduction

The number of people affected by diabetes mellitus (DM) is steadily increasing worldwide due to lifestyle changes (1). It is estimated to affect approximately 8.5% of the adult population, making it a global public health concern (2). In non-westernized nations, including Tunisia, the growing transition to urban living, westernized lifestyles, and the aging population have created conditions for the continuous growth of DM prevalence (3).
DM is associated with an increased risk of cardiovascular and non-cardiovascular morbidity, including cancers (4). Several studies have shown a correlation between DM and an increased risk of developing certain types of cancer, such as pancreatic cancer (5). Patients with DM have a two-fold increased risk of developing pancreatic cancer compared to the general population. Furthermore, individuals with newly diagnosed DM have a six to eight times higher risk of being diagnosed with pancreatic cancer within 36 months of their DM diagnosis. This highlights the importance of early detection and monitoring for pancreatic cancer in patients with DM (5). Pancreatic ductal adenocarcinoma (PDAC) is the most common malignant pancreatic tumor, accounting for over 90% of exocrine pancreatic cancers. Due to the advanced age of patients, retroperitoneal location of the tumor, nonspecific symptoms, and lack of screening recommendations, a large majority of patients with pancreatic cancer are diagnosed at late stages without any possibility of surgical intervention (6, 7). Although rare, the incidence of pancreatic cancer is steadily increasing, and its prognosis remains bleak with a significant risk of mortality (8). Therefore, a faster diagnosis is urgently needed.
The correlation between DM and pancreatic cancer, whether DM precedes pancreatic cancer or is rather a result of the disease itself, is still debated and requires further research to establish a more in-depth understanding of the underlying mechanisms (9).
The objectives of this study were to outline the epidemiological, clinical, and paraclinical features of diabetic patients who were subsequently diagnosed with pancreatic cancer, specifically PDAC, as well as to compare these features between those with newly diagnosed DM and those with long-standing DM.

Methods

A multicenter retrospective study was conducted in the region of Sousse, Tunisia, including patients with DM and exocrine pancreatic cancer of the adenocarcinoma type. The data was collected from the Endocrinology, Gastroenterology, Oncology, and General Surgery Departments at Farhat Hached University Hospital, as well as the Gastroenterology and General Surgery Departments at Sahloul University Hospital over 13 years from January 2010 to December 2022.
The diagnosis of DM was made according to the 2023 American Diabetes Association diagnostic criteria (10). PDAC was histologically confirmed on resected tissue, tumor biopsy, or metastases biopsy. The patients were followed up at consultations or hospitalized at the university hospitals of Sousse. We did not include other histological types of pancreatic cancer and patients with incomplete medical records.
Data on patients diagnosed with PDAC were gathered from the Cancer Registry of the Tunisian Center. Subsequently, we reviewed their medical records to identify any recent onset of DM, epidemiological characteristics of the patients, lifestyle habits, and clinical and paraclinical data including the results of various morphological examinations. Patients with PDAC who had newly diagnosed DM for less than three years were categorized as having newly diagnosed DM. The other patients were classified as having long-standing DM.
The collected Data were analyzed using GNU PSPP statistics software. Frequency and percentages were calculated for qualitative variables. Means and standard deviations were calculated for quantitative variables. Statistical comparisons of two means were conducted using a two-tailed Student's t-test. Statistical comparisons of percentages were performed using the chi-square test. Values < 0.05 were considered statistically significant in all statistical tests.
The study was approved by the ethics committee of the Faculty of Medicine of Sousse (Reference: CEFMS 264/2024).

Results

A total of 307 patients diagnosed with pancreatic cancer were identified from the Cancer Registry of the Tunisian Center, with 86% of cases being PDAC (Figure 1).
The prevalence of DM among patients with PDAC was 44.6% (118 patients). Of the 109 patients with full records included in the study, 45.87% (50 patients) were newly diagnosed with DM and 54.13% (59 patients) had a history of long-standing DM (Table 1).
The average age of the diabetic patients with PDAC was 63.9 ± 8.9, ranging from 36 to 89 years old. Most patients (98%) were aged 50 or older. Patients in both groups were predominantly male, with no difference between the mean age of both sexes ($p = 0.1$).
In patients with long-standing DM, the mean duration of DM was 11.7 ± 6.7 years [4–28] before the diagnosis of PDAC, mostly having type 2 DM (78%). Chronic

complications of DM were present in 22% of cases, mainly retinopathy (15.6%) and peripheral neuropathy (11%) (Table 1).

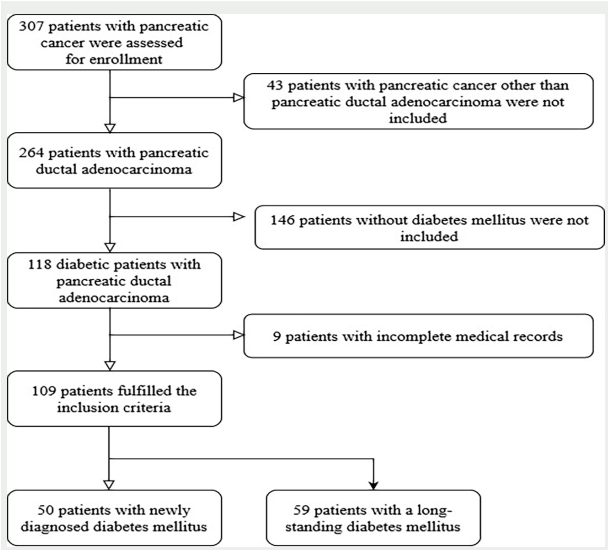

Figure 1. Flow diagram for study participants

Table 1. Clinical characteristics of Tunisian diabetic patients with pancreatic ductal adenocarcinoma.

Patients' clinical characteristics	
Age (years)	63.9 ± 8.9
Males (%)	72.5
Females (%)	27.5
Newly diagnosed diabetes (%)	45.87
Long-standing diabetes (%)	54.13
- Type 1	22
- Type 2	78
Diabetes complications (%)	22
- Retinopathy	15.6
- Neuropathy	11
- Cardiovascular diseases	4.6
- Nephropathy	2.8
Hypertension (%)	37.6
Smoking (%)	58.7
Alcohol consumption (%)	45
Body mass index (Kg/m^2)	25.4 ± 5.1

Family history of DM and pancreatic cancer was found in only 10.5% and 2.75% respectively of diabetic patients with PDAC and in 8% and 2% of newly diagnosed DM cases.

Six patients (5.5%) had a history of gallbladder lithiasis including three patients newly diagnosed with DM. Four of these patients had cholecystectomy. Chronic alcoholic pancreatitis was reported in three patients with long-standing DM. The duration between the diagnosis of chronic pancreatitis and that of cancer was 3 years on average.

Dyslipidemia was present in 11.9% of cases with 10% having newly diagnosed DM. Most patients (58.7%) were smokers, and the mean tobacco usage was 41.8 ± 26.4 pack-years. Alcohol consumption was reported in 45% of cases, with an average duration of 19.26 ± 13 years. Physical activity was regularly practiced in only 7.3% of cases.

The patients of the study were mostly obese (44%) or overweight (46.8%) with an average BMI of 30.9 ± 5 Kg/m² before the diagnosis of PDAC. Weight loss was noted in most patients (94.5%). The average amount of weight lost before the onset of cancer was 12.8 ± 6.3 kg, ranging from 2 to 32 kg. The weight loss occurred 1.5 months (median, IQR: 1–95) before diagnosis. A BMI less than 25 Kg/m² was found in half of patients on PDAC diagnosis.

Diabetic patients were treated with insulin in 64.2% of all cases and 88% of newly diagnosed DM cases. The remaining patients were on oral hypoglycemic agents, namely metformin prescribed in 56.9% of subjects. The biological assessment revealed uncontrolled DM with 89.9% of patients having glycated hemoglobin (A1c) levels equal to or greater than 8% (Table 2).

Table 2. Paraclinical characteristics of Tunisian diabetic patients with pancreatic ductal adenocarcinoma.

Patients' paraclinical characteristics	
Fasting glycemia (mmol/L)	14.8 ± 5.1
Glycated hemoglobin (A1c) (%)	10.5 ± 1.7
Accelerated Erythrocyte Sedimentation Rate (%)	37.9
Hepatic cytolysis (%)	50.4
Hepatic cholestasis (%)	52.3
Hyperbilirubinemia (%)	63.3
Hypercholesterolemia (%)	21.5
Hypo-HDL-cholesterolemia (%)	72.9
Hypertriglyceridemia (%)	29.7
Increased Cancer Antigen 19-9 (%)	71.4
Increased Carcinoembryonic antigen (%)	70.7
Blood group (%)	
- O	71.4
- A	19.6
- B	8.9
Tumor size (mm)	37.9 ± 13.1
Metastases (%)	78
Metastases sites (%)	
- Liver	72.9
- Lymph nodes	17.6
- Lungs	5.9
- Bones	3.5

The blood group was recorded in 51.3% of the cases, with type O being the most common, accounting for 71.4%. Hepatic cytolysis and cholestasis were observed in roughly half of the patients. Hyperbilirubinemia, predominantly conjugated form, was found in 63.3% of cases. The number of patients exhibiting elevated levels of Cancer Antigen 19-9 was comparable to those with positive Carcinoembryonic antigen results (Table 2).

The tumor sizes varied from 20 to 89 mm, with 72.47% of cases exhibiting tumors larger than 30 mm. At the time of diagnosis, the PDAC was classified as potentially resectable in only 13.76% of patients. It was metastatic in 78% of cases, predominantly in the liver (72.9%) (Table 2).

A comparison of clinical and paraclinical characteristics between patients with newly diagnosed DM and those with long-standing DM was conducted. Univariate analysis of these parameters revealed significant differences in drinking patterns and tumor size (Table 3). Patients with

long-standing DM had regular alcohol consumption (p = 0.03) and larger tumor size (p = 0.018). Analyzing the subgroup of men revealed that smoking more than 50 pack-years was also significant when compared to males with newly diagnosed diabetes mellitus.

In multivariate analysis, it was confirmed that regular alcohol consumption (p = 0.03), tumor size (p = 0.003), and males smoking more than 50 pack-years (p = 0.044) had an independent association with long-standing diabetes.

Table 3. Comparison of clinical and paraclinical characteristics between long-term and newly diagnosed diabetes in Tunisian patients with pancreatic ductal adenocarcinoma

Characteristics	Univariate analysis			Multivariate analysis	
	Newly diagnosed diabetes (n=50)	Long-standing diabetes (n=59)	p	OR (95% CI)	p
Age (years)	63.4 ± 8.1	64.3 ± 9.6	0.62		
Male (%)	76	69.5	0.45		
Female (%)	24	30.5			
Smoking (%)	62	55.9	0.53		
Male smoking > 50 pack-year (%)	15	45	**0.038**	0.32 (0.01-0.7)	**0.044**
Drinking patterns: (%)			**0.03**	0,3 (0,02-0,58)	**0.03**
- Occasional	70.6	36.4			
- Regular	29.4	63.6			
Hypertension (%)	38	37.3	0.93		
Body mass index (Kg/m²)	24.9 ± 4.8	25.9 ± 5.4	0.35		
Fasting glycemia (mmol/L)	14 ± 3.7	15.5 ± 5.9	0.14		
A1c (%)	10.4 ± 1.8	10.6 ± 1.6	0.59		
Weight loss (%)	92	96.6	0.41		
Abdominal pain (%)	62	50.8	0.24		
Jaundice (%)	54%	45.8	0.39		
Pancreatic ductal adenocarcinoma locations: (%)			0.51		
- Head	16	18,6			
- Body	72	59.3			
- Tail	12	22			
Tumor size: (%)			**0.018**	0,43 (0,15-0,72)	**0.003**
- ≤ 40 mm	76	54.2			
- > 40 mm	24	45.8			

Discussion

In our research, we found that 44.6% of patients diagnosed with PDAC also had DM. The prevalence of DM in patients with pancreatic cancer in general can vary in the literature depending on the methods used. Studies that actively screened patients for DM, like ours, reported a higher prevalence ranging from 38.1% to 65% compared to studies that used review of medical records or self-report methods (4–23%) (11, 12).

The prevalence of newly diagnosed DM in our PDAC patients was 45.87%. This prevalence varies depending on the duration of DM before the diagnosis of pancreatic cancer. In the study of Pannala et al., 75% of patients had a newly diagnosed DM for less than two years (12). Amri et al. reported that 42.7% of the patients were diagnosed with DM in the year preceding the diagnosis of pancreatic cancer (11).

Pancreatic cancer is uncommon among young adults and peaks between the ages of 70 and 80. It occurs slightly more frequently in males, with a reported male-to-female ratio of 1.3 to 1 (5). In our diabetic patients with PDAC a male predominance was observed, with a male-to-female ratio of 2.6:1. Their average age was 63.9 ± 8.9, and 98% were 50 years old or older. These results align with the findings of several investigations, ranging from 62,6 ± 1,5 to 68 ± 10 (11-13). Individuals aged over 50 years with newly diagnosed DM are known to have a 6 to 8 times higher risk of being diagnosed with pancreatic cancer within 3 years following the diagnosis of DM, with a 3-year incidence of pancreatic cancer of approximately 1% (5, 14). This has led to the idea that newly diagnosed DM could serve as a potential clue for early detection of pancreatic cancer, yet it is not recommended for asymptomatic adults due to the very low incidence of pancreatic cancer compared to DM and the lack of a safe and effective screening method for pancreatic cancer (5, 15).

Additional risk factors were suggested to help better define the population of newly diagnosed DM who require more thorough screening (16). Gallstones, chronic pancreatitis, and a family history of pancreatic cancer are considered the main non-modifiable risk factors for pancreatic cancer (5). A higher risk of pancreatic cancer in newly diagnosed DM patients was also noted in the case of dyslipidemia (17). In our diabetic Tunisian population with PDAC, only a limited number of patients had a history of chronic pancreatitis (2.7%), gallstones (5.5%), and dyslipidemia (11.9%). A family history of pancreatic cancer was found in one patient, which was consistent with the literature reporting that most pancreatic cancer cases arise sporadically with limited family history (5).

Alcohol consumption and tobacco use are both well-established risk factors for the development of pancreatic cancer (5). These addictions were found in 45% and 58.7% of cases respectively in our study. Tunisian patients with newly diagnosed DM were drinking occasionally compared to those with long-standing DM who were drinking regularly and were also heavy smokers. These results were confirmed by multivariate analysis for the population for alcohol consumption and the male subgroup for tobacco use.

Patients with newly diagnosed DM who are not obese are 1.72 more likely to be diagnosed with pancreatic cancer within 3 years of their DM diagnosis (18). In our study, only 9.2% of patients had a BMI below 25 Kg/m² before the diagnosis of PDAC and that number rose to approximately 50% at the time of diagnosis as a result of weight loss. Weight loss precedes other specific symptoms of pancreatic cancer at the onset of DM (19). Both weight loss and newly diagnosed DM were attributed to a paraneoplastic secretion, therefore, they are of great value in diagnosing pancreatic cancer (19, 20).

Tumor markers such as Cancer Antigen 19-9 and serum bilirubin levels may serve as a useful biomarker for pancreatic cancer particularly in asymptomatic patients. When either of these levels is elevated, appropriate imaging studies should be conducted (21). In our population, most patients had hyperbilirubinemia or increased tumor markers. Nevertheless, no significant differences were identified between patients with newly diagnosed DM and long-standing DM.

In the literature, it has been reported that there was no significant association between diabetes and the size, location, or stage of the cancer (12). Furthermore, in our series, there were no significant differences between the tumor location and metastase sites, but patients with newly diagnosed DM had a smaller tumor size compared to those with long-standing DM.

The limitations of this study include its retrospective design and the incomplete data present in the medical records. The research was conducted exclusively within the Sousse region. However, Sousse is the third most populous region in Tunisia and is home to two university hospitals that serve as reference centers for cancer and surgery in the country.

In summary, our study highlighted many similarities between newly diagnosed DM (or type 3c DM) and long-standing DM in PDAC patients suggesting a shared underlying basis for both conditions.

PDAC should be particularly considered in patients over 50 who have recently been diagnosed with DM, especially if they exhibit occasional drinking habits and are not heavy smokers for males. Recognizing these risk factors can facilitate earlier detection of PDAC, potentially improving the prognosis of the disease.

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