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Association of Diabetes Mellitus and Pancreatic Cancer: Literature Review

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Abstract: Despite the metabolic activity, mainly related to endocrinological disease, diabetes mellitus seems to be associated with pancreatic cancer. Studies in this line of research are still limited and without a detailed description of the disorders that confirm the association between them. Thus, the present study aims, through a narrative review, to present the association of pancreatic neoplasia and diabetes mellitus, evaluating the mechanism of association between the endocrinological presentation studied as a causal factor or possible consequence of the neoplastic condition, as well as evaluating the possibility of screening against pancreatic neoplasia, which has one of the highest rates of mortality already described in the literature.

Keywords: Pancreatic Cancer; Oncology; Diabetes Mellitus; Endocrinology.

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1. Introduction

Pancreatic cancer (PC), a neoplasia represented by the Adenocarcinoma subtype in 90% to 95% of cases, consisting of a higher diagnostic prevalence for males over 60 years, a tumor subtype intrinsically associated with somatic causes [1-7]. In Brazil, according to the National Cancer Institute (INCA), Pancreatic Adenocarcinoma (PA) is responsible for about 4% of neoplasm mortality and responsible 2% of all diagnoses among solid tumors [2]. PA is a solid tumor composed of similar incidence and mortality rates, which translates into high lethality, and life expectancy is approximately 5% in 5 years, in most cases the diagnosis occurs in advanced stages, corroborating in metastatic presentations [1, 4].

Once the pancreas has an important endocrine function, the evolution of the tumor consequently leads to failure in the production of intrinsic metabolic substances. In advanced stages of the disease or after complex surgeries, we observe the development of steatorrhea and symptoms related to hyperglycemia, diabetes mellitus and metabolic syndrome as risk factors for the PA [4,6]. In fact, diabetes mellitus is present in most patients with PC during the diagnosis and evolution of the disease [3-5].

This question highlights the importance of clinical investigation to good glycemic management and active search for fasting blood glucose and glycated hemoglobin levels throughout treatment, despite special attention to symptom control and the need for good caloric intake with weight maintenance and nutritional index and less the late

complications of diabetes that these patients will not experience [4, 7]. Despite the metabolic activity, especially related to endocrinological disease, diabetes mellitus seems to be intrinsically associated with the pancreatic neoplasm condition. Studies in this line of research are still scarce and without a detailed description of the mechanisms that confirm the association between such diseases [6, 7]. Our research group also pose a scientific inquiry that has been deliberated by the group, regarding whether individuals with diabetes, particularly those with recent diagnoses or presenting with greater challenges in glycemic control, warrant active surveillance for neoplastic growth. This proactive approach may lead to earlier diagnoses and more effective curative treatment options for these patients [5-7].

Thus, the present study aims, through the narrative review, to report the association of pancreatic neoplasia and diabetes mellitus, seeking to evaluate the mechanism of association between the endocrinological presentation studied as a causality factor or possible consequence in the face of the neoplasm condition.

2. Pancreatic cancer

Pancreatic cancer (PC) is a neoplastic disease, with Adenocarcinoma representing 90% to 95% of cases. It is more commonly diagnosed in males over the age of 60 and in black ethnicity, intrinsically associated with smoking, obesity and alcoholism, somatic causes [1-3, 5-7]. Genetic factors such as Peutz-Jeghers syndrome and hereditary pancreatitis, as well as germinal order survival represented by alterations in *BRCA1*, *BRCA2*, *p16*, *ATM*, *STK11*, *PRSS1*, *PRSS2*, *SPINK1*, and *PALB2*, have been associated with pancreatic carcinogenesis [4, 5].

Based on the information provided by the National Cancer Institute (INCA), in Brazil, this carcinogenic subtype of cancer that accounts for about 2% of all diagnoses among solid tumors and is responsible for 4% of neoplastic mortality [2]. According to a European epidemiological study, pancreatic cancer has the fourth mortality rate among solid tumors, surpassed only by lung, colorectal and prostatic cancer in males and by breast, colorectal and lung cancer in females [5, 6].

A solid tumor with similar incidence and mortality rates, and a life expectancy of approximately 5% in 5 years, is often diagnosed late, at an advanced stage, which may support presentations associated with metastatic activity [3]. Approximately 15% to 20% of all patients are considered suitable candidates for the surgical procedure, and among these patients, the average survival rate is around 5 years [3]. This rate is higher, at about 25%, for patients without lymph node involvement, but drops to 10% for patients with evidence of lymph node involvement [3].

Despite advances in clinical research, the prognosis for pancreatic neoplasm remains reserved with no significant improvement over the past 20 years, locally advanced disease has an average survival rate of 8-12 months, while metastatic disease has a survival rate of up to 6 months. However, the Polo phase III study revealed that 4-5% of patients with germline mutations in *BRCA1* or *BRCA2*, who received platinum-based chemotherapy without disease progression, benefited from maintenance treatment with Olaparib, showing a significant increase in progression-free survival of 7.4 months compared to 3.8 months for those receiving placebo. Despite this progress, pancreatic neoplasm remains one of the most aggressive tumor subtypes in clinical oncology [8].

Given the limited progress in developing new treatments, it may be worthwhile to focus on screening higher risk groups for pancreatic neoplasm and exploring potentially curative treatment options. One such group that should be studied and better understood is the population with diabetes or metabolic syndrome.

3. Association of pancreatic cancer and diabetes mellitus: a bidirectional relationship

Pancreatic cancer and diabetes mellitus (DM) share common risk factors, including age, obesity, and insulin resistance. This suggests a bidirectional relationship between the

development of pancreatic cancer and diabetes mellitus, where one can be both a cause and consequence of the other. However, the mechanism of this association remains complex [9]. A Chinese study presented the pathophysiological aspects of the association between diabetes mellitus and pancreatic cancer. The study analyzed the altered profile of serum microRNAs in individuals with recent onset diabetes mellitus associated with pancreatic cancer, revealing the association with type 2 diabetes mellitus as one of the main factors in the development of the disease [10].

This data supports diabetes as a causal factor of pancreatic cancer. However, it is important to note that although less common, type 3c diabetes, which is of exocrine origin, is also frequently associated with pancreatic ductal adenocarcinoma. This type of diabetes usually occurs in more advanced stages of the neoplasm and is often accompanied by other signs of pancreatic failure [11]. Lu et al. study presented the relationship between an increase in HbA1c levels and an increased risk of pancreatic cancer. The study demonstrated that hyperinsulinemia and insulin resistance contribute to the damage to the pancreatic organ. Initially, an increase in insulin production occurs as a response to combat insulin resistance, which are considered pathophysiological factors directly linked to the development of neoplasms [12].

A European multicenter randomized study evaluated the association between diabetes mellitus and pancreatic neoplasia. The study consisted of 1,440 patients who were divided into two comparative groups. One group was diagnosed with pancreatic malignancy, and the other control group consisted of patients without comorbidities [13]. The group with a history of pancreatic neoplasia had a higher prevalence of diabetes mellitus, at 22.8%, compared to only 8.3% in the placebo group. It is noteworthy that in approximately 56% of the patients included in the neoplastic group, the endocrinological condition was diagnosed 2 years before the neoplasm. Evaluating the entire study, 40% of the patients included in the diabetes group were diagnosed together with the neoplastic case. These data reinforce the relationship between the development of cancer in patients with previously diagnosed diabetes [13].

The Swedish prospective study, which included 130,000 patients with type 2 diabetes with a minimum duration of 2 years, concluded that approximately 650 of the patients included in the study were diagnosed with confirmed pancreatic cancer. The study concludes that the endocrinological condition studied is a risk factor for the development of pancreatic cancer [14].

A veterinary study performed with hamsters with pancreatic neoplasms induced by nitrozamide found that animals fed a diet rich in fat develop greater pancreatic neoplastic potential after drug induction, as such associative factors may be linked to the state of insulin resistance, which in the study suggests that the pancreatic beta cells may be involved in carcinogenesis [15]. Another study performed with hamsters, evaluated the prevention of pancreatic cancer through metformin, a study in which it defines hyperplasia of pancreatic islet beta cells, insulin resistance and, consequently, the development of pancreatic malignancy, mainly ductal carcinoma [16]. It is noteworthy that the group of hamsters fed in the study with a diet rich or not in fat, both using metformin, showed a lower rate of carcinogenic development, around 43% of the studied population [16].

Duan et al. conducted a study on treatment methods for diabetes and found that short-term insulin therapy (less than 5 years) was associated with an increased risk of pancreatic cancer, while long-term insulin use did not show a significant association. They also suggested that long-term use of oral antidiabetic drugs, such as metformin, may have a preventive effect against pancreatic cancer [17]. The progression of the disease tends to affect the pancreatic head, which is the right side of the organ, although other regions may also be affected. In terms of metastatic activity, particular attention should be paid to the involvement of the liver [18-19].

The progression of the associated endocrine disease is a crucial factor to consider, as it can lead to pancreatic exocrine insufficiency. This condition affects approximately 32% of diabetic patients and can be exacerbated in the presence of pancreatic neoplasms. The

main treatment approach for this condition involves the use of enzyme supplements that contain pancreolipases [13]. In a recent study, the survival approach was to evaluate the overall survival of patients with pancreatic cancer who had a pre-existing diagnosis of diabetes mellitus (DM). The study confirmed that the endocrine disease is associated with the development of pancreatic neoplasia and can also lead to an increased risk of mortality. The study demonstrated a reduction in overall survival of approximately 1.2 months in patients with diabetes mellitus compared to those without an endocrine disorder [20].

Therefore, although less frequent than other risk factors such as smoking and alcoholism, screening for early detection among patients with associated endocrine diseases is a possibility that should be considered. This is because approximately 1% of patients with a recent diagnosis of DM will develop pancreatic neoplasia within 3 years. Further steps in this review should include cost analysis and evaluation of clinical applicability.

The potential causal relationship and earlier detection of pancreatic neoplasia in patients with pre-existing diabetes mellitus justifies further studies to design a screening protocol for these patients. The aim of such a protocol would be to enable early diagnosis of pancreatic neoplasia, considering glycemic levels, markers, and imaging tests. Additionally, this would help to elucidate the optimal diagnostic methods for identifying pancreatic neoplasia in patients with diabetes mellitus.

3. Impact of the surgical approach on the clinical presentation association

There are few studies that have investigated the surgical approach in patients with pancreatic neoplasms and a history of diabetes mellitus. However, one notable study published by Permert et al. suggests that diabetes mellitus associated with pancreatic neoplasia is essentially insulin-resistant diabetes. The study also indicates that surgical removal of the neoplastic lesion can eliminate the factor that causes insulin resistance [22-24]. This study reinforces the idea that the presence of a pancreatic neoplasm can be a causal factor in the development of diabetes mellitus. The researchers argue that the mechanism triggering this condition is associated with the production of factors by the pancreatic neoplasm, particularly amylin, which increases the production of pancreatic beta cells and contributes to insulin resistance [22-24].

The initial study conducted by the group of researchers aimed to evaluate glucose metabolic activity in 44 patients diagnosed with pancreatic neoplasms compared to a control group of 8 patients without any comorbidities [22]. The study resulted in the finding that approximately 64% of patients in the neoplastic group had a confirmed diagnosis of diabetes mellitus, while 11% had glucose intolerance [22]. Thus, confirming the association between the diseases.

In a second study conducted by the group of researchers, they included a total of 7 patients with pancreatic cancer measuring between 2 to 3 cm, who underwent complete tumor resection. The researchers analyzed the characteristics of the patients before and after the procedure and concluded that 6 out of 7 participants had a previous endocrinological diagnosis of diabetes before the surgical procedure. After the procedure, only 4 patients maintained an endocrinological alteration, with 2 patients using oral drugs for control and the other 2 requiring insulin control [23]. The data favor the idea that endocrinological disease can be considered a predisposing factor for pancreatic neoplasms. However, with surgical removal of the neoplasm, the patient's endocrinological condition can significantly improve, according to clinical indications.

In the third study conducted by Permert et al., the secretion of pancreatic hormones, especially amylin, was evaluated in 30 patients with pancreatic cancer before and after surgical resection and compared with a control group composed of patients with other types of cancer such as lung, liver, and colon cancer [24]. It was possible to observe that around 70% of the patients in the neoplastic group presented glucogenic alterations, and approximately 60% of these had confirmed association with diabetes, while 10% showed glucose intolerance. Additionally, amylin markers were found to be higher in this association with the disease [24].

4. Conclusion

Based on the analysis of the reviewed data, it is evident that diabetes mellitus is an independent risk factor for the development of pancreatic neoplasia and its complications. This association is mainly due to mechanisms such as hyperinsulinemia, insulin resistance, and genetic damage, as described by experimental studies. Recent-onset diabetes mellitus is considered an early marker for pancreatic cancer, while short-term diabetes mellitus treated with insulin therapy increases the risk of pancreatic cancer. The association between these two diseases is linked to reduced overall survival and increased mortality. Therefore, it is crucial to continue researching this topic to develop effective screening strategies for early detection of pancreatic cancer in diabetic patients.

Currently, there is no established protocol for screening diabetic patients for pancreatic cancer. However, the data analyzed in this review suggest a clear association between diabetes mellitus and pancreatic cancer, highlighting the importance of considering the possibility of malignancy in these patients, particularly with regards to glycemic control as a potential screening factor. Further research is needed to confirm and validate these findings, and to develop effective screening strategies for early detection of pancreatic cancer in diabetic patients.

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