The Influence of Diabetes Mellitus in Development and Prognostic of Pancreatic Neoplasia

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Pancreatic cancer is one of the most aggressive malignant diseases due high rate of recurrence and the lack effective medical therapy. Surgery remains the only option for curable treatment but unfortunately, less than 20% of patients are eligibles at the time of diagnosis therefore identifying the risk factors represent a big step for cancer research. Pancreatic cancer is frequently associated with diabetes or glucose intolerance. There are two hypotheses at the base of this observation: either the diabetes cause pancreatic cancer or is a concequences of the cancer. In these theses we studied the patients diagnosticated with pancreatic cancer and with diabetes mellitus type 2. A total of 256 pancreatic cancer cases were identified and 71 patients had diabetes mellitus and 21 patients had glucose intolerance. Mean age 62.2 years, 81% cases were male and in 71% cancer originated form the pancreatic head. In 51.4% cases the diagnosis was in stage IV of the disease. Patients with pancreatic cancer and diabetes mellitus had reduced survival compared with those without diabetes but the difference was not statistically significant. Diabetes mellitus is associated with a decreased survival among patients with pancreatic cancer and reveal a link between chronic glucose intolerance and pancreatic cancer survival. The complex relationship between pancreatic cancer and diabetes requires more clinical research in order to developed new therapeutical posibilities.

Keywords: pancreatic cancer, diabetes mielitus, survival, glucose intolerance

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Pancreatic cancer is currently one of the most fatal malignant diseases due to the late diagnosis, high rate of recurrence and the lack effective medical therapy [1]. In this moment, surgery remains the only curable treatment option. Unfortunately, less than 20% of patients are eligibles for surgery at the time of diagnosis and even in this situation the median postoperative survival is under 20 months with a 5-year survival of approximately 20% [2]. Pancreaticoduodenectomy (PD) is the most common procedure performed for pancreatic cancer and is a challenging procedure operformed for tumors of pancreatic head associated with a perioperative morbidity of 30% Today, pancreaticoduodenectomy (PD) is and it is carried out routinely at high-volume centers with mortality rates <2% [3].

The symptoms of pancreatic cancer are nonspecific, such as abdominal pain, fatigue, nausea, weight loss and jaundice and may present themself late in the course of the disease and thereby the diagnosis is usually revealed in advanced stages, after locally invasions or systemic dissemination [4]. The etiology of pancreatic cancer is incompletely understood and the identification of the risk factors mainly the ones that are modifiable through behavioral change or medication, remains a point of interest in the study of this disease. The risk factors implicated in development of pancreatic cancer include family history, smoking, chronic pancreatitis, obesity and diabetes mellitus.

Phthalates are commonly used in products such as cosmetics, soaps, pesticides, lubricants, plastics, and paints. Studies have also found associations between some phthalate metabolites and antiandrogenic effects in humans, including both infant and adult males. The researchers compared the levels of phthalates in the samples with the prevalence of chronic diseases in their subjects and also promote *tumori genesis* in a variety of cell types through AhR-mediated genomic and nongenomic pathways. They found that the men who had higher levels of phthalates had higher rates of cardiovascular disease, hypertension and type II diabetes .Finally, they adjusted the results to allow for differences in lifestyle, socioeconomic factors, and overweight and obesity. They found the results to still be significant [5, 6].

The relationship between pancreatic cancer and diabetes is complex and long debated. Various studies have revealed an increased risk of pancreatic cancer among patients with long-standing diabetes with a parallel increase in the prevalence of type 2 diabetes mellitus and in the incidence of PC. Population studies identified that about half of patients with pancreatic cancer have diabetes mellitus at the time of diagnosis. The factors implicated in development of pancreatic cancer appear to be the chronic metabolic and inflammatory repercussions of diabetes [7].

Recent studies indicated that roughly 20-30% of patients with pancreatic cancer developed diabetes in the 2 to 4 years prior to the neoplastic diagnosis [8, 9]. Hyperglycemia can be secondary to pancreatic tumor secret factors that cause paraneoplastic modification and recent onset diabetes will be treated by the surgical tumor resection [10].

In these theses we studied the relationship between pancreatic cancer and diabetes in order to assess if diabetes is cause or consequence of pancreatic neoplastic lesions.

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Experimental part

We evaluated patients with pancreatic cancer and diabetes mellitus or glucose intolerance admitted in our Surgical Unit between January 1, 2012 and December 31, 2016. We included in this study only the patients with clinic, imagistic, laboratory and morphopathological diagnosis of pancreatic neoplastic disease. The socio-demographic data related to age, gender, residence, smoking habits, and family and personal medical history and treatment were collected from hospital database.

The data were processed using IBM SPSS Statistics and the statistical analysis was made with Anova, Student's T-test, chi-square test and Fisher test in order to assess the quantitative and qualitative variables between the collected data. The result were considered statistically significant if *p* was less than 0.05 and a 95% confidence interval.

Results and discussions

A total of 256 pancreatic cancer cases were identified and 71 patients had diabetes mellitus and 21 patients had glucose intolerance. Mean age 62.2 years, 81% cases were male and in 71% cancer originated form the pancreatic head. In 51.4% cases the diagnosis was in stage IV of the disease (table 1).

Table 1
PATIENT CHARACTERISTICS

Patient characteristic	
Mean age (SD), years	62.2
Males, n (%)	207 (81)
ASA classification n (%)	
I	36
II	49
III-IV	15
Co-morbidity, n (%)	
Cardiac	28(11)
Hypertension	46(18)
Pulmonary	10(4)
Diabetes mellitus	71 (28)
Glucose intolerance	21(4.7)
Body index mass (mean)	25.7
Tumor location, n (%)	
Head	182(71)
Body	16(6.4)
Tail	58(22.6)
Cancer stage, n (%)	
Localized	76 (29.5)
Locally advanced	49(19.1)
Metastatic	131(51.4)
Median survival, months	
Localized	23
Locally advanced	13
Metastatic	7
Overall survival	10.9
With diabetes mellitus	9.1 p-value 0.53
Non-diabetes mellitus	10.6

For the local disease the treatment implied tumor resection and lymphadenectomy.

In two patients with locally advanced stage due to oncological reasons was required resection of a totally replaced common hepatic and reconstruction using a reversed splenic artery.

For the other cases of locally advanced or metastatic disease were performed palleative procedures in order to treat the jaundice, duodenal obstruction or pain consequently to celiac trank invasion.

In the selected group, the patients had in 29% localized disease, 19.1% had locally advanced disease, and 51.4% had metastatic disease. The median survival times were 23 months for patients with localized, 13 months for those with locally advanced and 7 months for those with metastatic disease. By the end of the follow-up 91% of patients had died.

Patients with pancreatic cancer and diabetes mellitus had reduced survival compared with those without diabetes but the difference was not statistically significant. The glucose intolerance diagnosed prior or at the time of cancer confirmation had no impact in patient prognostic and the pancreatic resection had no influence in postoperative glycemic levels.

Cancer represents one of the most important pathological manifestations at worldwide level, being characterized by an extremely complex etiology, inducing highly diverse associated complications of physiological, metabolic or biochemical nature [11-15].

In the pathology of tumors, there are several reasons in favor of immunology. Spontaneous regressions of malignant tumors and of their metastases have been reported, as well as an increased incidence of neoplasia in immuno-depression. One of the main functions of the immunity system in neoplastic pathology consists in the detection and purging of new tumoral cells. The paradox of immunology is that, often, the immunitary system favors tumoral development rather than its inhibition [16]. Blocking of normal cell mechanisms of apoptosis, followed by uncontrolled proliferation, leads to the formation of cancer cells populations [17].

Pancreatic cancer is a life-threatening disease with an overall 5-year survival rate about 6% and a median survival rate that varies from approximately 2 years in resectable disease to few month in case of locally advanced or metastatic disease [18]. Because the advance stage in time of the diagnosis only about 20% of patients are candidates for surgery [2].

In order to reduce de mortality associated with this disease the key is an early diagnosis, treat the precursor disease and identifying the risk factors that are modifiable [2, 19]. The goal is to identify the high-grade precursor lesions and/or early invasive pancreatic cancer in order to obtain the most benefits from surgical resection [20]. The findings of definitive biomarkers are not available, but further research will hopefully lead to the identification of biomarkers that indicate high-grade dysplasia or transition to invasive growth [19]. Butler et al. [21] studied the effect of diabetes mellitus on pancreatic cancer in this research of the expression of the neoplastic markers cytokeratin and Ki67 in pancreatic ductal epithelia from 45 human autopsy and nine surgical pathology specimens. They observed that in obese diabetics the duct epithelial replication was increased compared with nondiabetic subjects indicating an effect of obesity and long-standing diabetes on the replication rate and therefore in development of pancreatic cancer. In the surgical specimens or in the non-tumor tissue surrounding cancer cells were observed even higher rates of replication markers implying the role of these factors in carcinogenesis [21].

Despite the latest studies indicate that diabetes mellitus is associated with an increased risk of pancreatic cancer, the pathological mechanism of diabetes-related have not been yet elucidated. It seems that glucose resistance and compensatory hyperinsulinemia represent the me mechanisms associated with diabetes and development of pancreatic cancer and several epidemiological studies revealed also an increased risk for other malignancies,

including carcinomas of the breast, prostate, colon, and kidney [22, 23].

Hyperglycaemia is an initiating event leading to a series of metabolic changes that may originate from increased oxidative stress [24]. The hyperglycemia induced by increased oxidative stress and receptor for advanced glycation end products (RAGE) activation increases the activation of transcription factor-jB (NF-jB) in endothelial and vascular smooth muscle cells.

This transcription factor regulates the expression of the genes encoding a number of mediators of atherogenesis such as leukocyte-cell adhesion molecules and chemoattractant proteins that recruit lymphocytes and monocytes into the vascular wall [25]. Also, oxygen free radicals (superoxide anion, hydroxyl radical etc) produced in excess stimulate lipid peroxidation of the polyunsaturated fatty acids forming, thus, in excess, lipid-peroxil radicals [26].

Many studies indicated that 25% to 50% of the patients diagnosed with pancreatic cancer will have developed diabetes within less than 3 years prior the malignancy ascertained and suggest that diabetes mellitus might be a biomarker of early-stage PC [24]. The new-on-set diabetes is not a individual predictor of pancreatic cancer and can be the only indication for radiological or endoscopic screening, because about 98% of patients diabetes will never develop pancreatic cancer and the screening did not result to be either practical or reliable as an early detection method [27, 28].

A meta-analysis of 20 studies about the relation between pancreatic cancer and diabetes examined by Everhart et al. [29] identified a relative risk from of 2.1 for diabetes with a duration of at least, l year prior to neoplastic diagnosis and 2.0 for diabetes with a duration of at least 5 years and the conclusion was that cancer could be added to the list of complications of diabetes and also found an increased risk of dying due to pancreatic cancer among diabetics or those with glucose intolerance, compared with those without diabetes [30-32]. We observed a small difference in survival for patients with diabetes compared with those without diabetes but this difference was not statistically significant.

Conclusions

The mechanism implicated in the association of pancreatic cancer and diabetes is not completely elucidated but can offer new pathways for therapeutic opportunity. Diabetes mellitus was associated with a decreased survival among patients with pancreatic cancer and reveal a link between chronic glucose intolerance and pancreatic cancer survival. The complex relationship between pancreatic cancer and diabetes requires more clinical research. Also reducing the risk of pancreatic cancer might be obtained by prevention and treatment of diabetes and early detection of tumors in resectable stages.

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