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Original paper

Type II Diabetes Mellitus - Associated Risk Factor in the Onset and Evolution of Digestive Tract Carcinoma

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Abstract

Introduction: The number of digestive cancers cases has alarmingly increased within the past decades up to a current third place ranking in terms of global incidence. The association between type II diabetes mellitus and digestive neoplasms has been on an upward trend lately due to common risk factors as well as to mutually potentiating effects on the evolution of the two conditions.

Patients and methods: This clinical study evaluates a group of 34 gastro intestinal cancer patients suffering from type II diabetes mellitus who received treatment in 'Elias University Emergency Hospital', Medical Oncology division, between 2010 and 2016. A number of demographic features specific to the aforementioned group, as well as comorbidities linked to localization, the aggressiveness of primary digestive tumor and the presence of the biological inflammatory syndrome were evaluated.

Discussion: Digestive neoplasms associated with type II diabetes mellitus turn out to be more aggressive. The therapy is burdened by potential risks arising from all associated pathologies.

Conclusions: A set of clinical and biological data underpin the association between type II diabetes mellitus and digestive neoplasms as being detrimental. Therefore, screening measures for digestive neoplasms in type II diabetes mellitus patients should be carefully respected.

Keywords : diabetes, digestive cancers, risk factor, inflammatory syndrome

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Introduction

The incidence of digestive cancers and diabetes has increased exponentially in the last decade. According to the International Diabetes Association [1], one out of 11 adults worldwide (415 million people) were diagnosed or were already suffering from diabetes. Of the many digestive tract cancer subtypes, colorectal cancer is the third most common cancer worldwide. Almost 1.4 million positive diagnosis were made in 2012, of which almost 95% being classified as adenocarcinomas [2]. Inquiries into any existing links between the two conditions have been made as early as 1959, starting with population-based studies. The majority of the later studies conducted have focused mainly on type 2 diabetes, since early data suggested that its presence increased the relative risk for digestive cancers to more than twofold (GIOVANNUCCI & al. [3]). Data shows that type 2 diabetes is strongly related to liver and pancreatic cancers (GIOVANNUCCI & al. [3]). Although the observed incidence numbers suggest this relation, it can also be stated that diabetes produces a number of hyperglycemia-related metabolic disorders, all of which directly impact the two organs. Moreover, given that diabetes is a worldwide underdiagnosed condition by a margin of at most 5%, this relation implies a higher cancer risk for the normal population (VIGNERI & al. [4]). Furthermore, some of the medications used for controlling diabetes have been shown to also have a negative link with certain types of cancer (NGUYEN& al. [5]). Although not entirely proven by the available data, this relationship has become more visible in recent years, given the existence of different types of drugs. It is important to note that the cancer risk for patients with uncontrolled diabetes is considerably higher than for patients with controlled disease (GIOVANNUCCI & al. [3]).

Type II diabetes is also linked both with a cytokine-induced inflammatory response and a long-term tissue necrosis response, which are considered to be relevant factors in determining either the relative risk of developing cancer or of the survival rate, for those already having a cancer-type condition (GIOVANNUCCI & al. [3]). As proven by other clinical studies, chronic inflammation facilitates tumor development and impairs the normal immune system response in an area, allowing for cancerous cells to proliferate [STANCIU & al. [6]). Thus, a chain of causality can be drawn starting from a diabetes condition that may lead to incidence or prognosis of cancers (LEROITH & al. [7]).

Materials and Methods

This work involved 34 patients with a history of type II diabetes mellitus, who were diagnosed with digestive tract neoplasms between 2010 and 2016 and who received treatment in “Elias University Emergency Hospital”, Medical Oncology division. The diagnosis of gastro-intestinal cancer was confirmed in all patients by histopathological results. All patients were initially evaluated by paraclinical (e.g. imagistic methods, such as computer tomography or magnetic resonance imaging - in selective patients), and by clinical findings. Individual data regarding sex, age at diagnosis, family history of diabetes and cancer, tobacco smoking, working in toxic environment and associated pathologies were collected. After receiving initial cancer treatment (surgery, chemotherapy or radiotherapy) the participants were re-evaluated. Tumor markers (CEA - carcinoembryonic antigen and CA 19-9 - carbohydrate antigen 19-9) and inflammatory markers (LDH - lactate dehydrogenase, ESR - erythrocyte sedimentation rate and CRP - C - reactive protein) were examined in correlation with tumor stage, evolution and response to oncological treatment.

Results and Discussions

Table 1 shows baseline characteristics of patients. Out of the 34 patients, more than 2/3 were men. Indexing the results by the age at cancer diagnosis, resulted that only one patient was diagnosed at an age lesser than 50 years old and 21 had over 65 years old at the time of the diagnosis. There was a family history of diabetes in 7 cases and a family history of cancer in 9 cases. From the latter group, only 3 patients had a family history of digestive tract cancers.

Tobacco smoking proved to be an inconclusive risk factor in developing gastro-intestinal cancers in patients with diabetes, given that the distribution of smokers and non-smokers was almost equal. On the same note, toxic working environments could not be looked upon as a risk factor in this study, given the small number of patients who have been exposed.

Table 1. Patient characteristics and diabetes treatment type

Characteristics	No patients
Sex distribution	
men	23
women	11
Age at cancer diagnosis	
< 50 years	1
50-64 years	12
>= 65 years	21
Family history of diabetes	
yes	7
no	27
Family history of cancer	
digestive cancers	3
other	6
none	25
Tobacco smoking	
current/ex-smokers	18
never smokers	16
Working in toxic environment	
yes	3
no	31
Current treatment for diabetes	
oral antidiabetics	22
insulin	8
diet only	4
Associated pathologies	
dyslipidemia	10
arterial hypertension	22
cardio-vascular diseases	20

Diabetes requires one or more drug types in order to control the disease. From the studied group, most participants (22) managed this condition by using oral antidiabetic medication, 8 were insulin dependent, while the rest (4) were only under dietary restrictions. Common comorbidities of diabetes mellitus were also present in the studied group. Most patients had a history of arterial hypertension (22) and/or heart disease (20). Dyslipidemia was observed in almost ¼ of cases.

Table 2. Primary tumor localization and tumor characteristics

	No patients	Percentage (%)
Types of cancer		
colorectal cancer	20	58.8
pancreatic cancer	9	26.4
gastric cancer	4	11.7
hepatocarcinoma	1	2.9
Tumor differentiation		
G1	8	23.5
G2	18	52.9
G3	6	17.6
undifferentiated	2	5.8
Tumor staging		
0	1	2.9
I	1	2.9
II	8	23.5
III	8	23.5
IV	16	47

Table 2 renders the distribution of digestive tract tumor primary sites, tumor staging and histological tumor differentiation. As previously mentioned, colorectal cancer has a wide incidence rate world-wide, that also reflects in the results of this study, being diagnosed in 58.8% of the patients, followed by pancreatic cancer at almost half the ratio (26.4%). Gastric and hepatic cancers were not as common as the previous two locations, all of them adding up to 14%. Tumor staging is an important factor that correlates with tumor prognosis and aggressiveness. Almost half of the patients presented metastases at diagnosis, while only 6% had early stage tumors. Tumor differentiation grade is another factor to take into consideration when

assessing prognosis. More than 50% of patients were diagnosed with moderately differentiated tumors.

As previously mentioned, 16 patients were diagnosed with metastases at the initial evaluation: 8 had colorectal cancer, 4 pancreatic cancer and 3 had gastric cancer. Table 3 concludes that hepatic metastases are the most prevalent, being present in 11 cases followed by lymphatic, pulmonary and peritoneal dissemination in almost equal distribution. Besides these, only 4 patients presented bone metastases.

Table 3. Location of metastases at diagnosis

Location of metastases at diagnosis
hepatic metastases
lymphatic metastases
pulmonary metastases
peritoneal metastases
bone metastases

Paraclinical investigations were conducted in order to determine a correlation between tumor staging, tumor markers and inflammatory markers. In early stage cancer patients (stages 0, I and II) these indicators had normal values at diagnosis. Similar results were also found in the majority of patients with stage III tumors. On the other hand, in metastatic cases, these values were elevated beyond normal ranges. In the case of tumor markers, from the total number of 16 patients who were diagnosed with metastases at the initial evaluation, 9 patients had (>1 time) elevated levels of CEA and 4 had (>2 times) elevated levels while in the case of CA19-9 marker, 14 patients had (>3 times) raised levels and 2 patients had (>2 times) raised levels. Inflammatory markers were also beyond normal ranges, 10 patients had elevated LDH levels (>2 times), 9 patients had raised ESR levels (>2 times) and 6 patients had elevated CRP levels (>1 time).

Diabetes diagnosis rates are increasing worldwide and, from a sex distribution standpoint, are fairly balanced. Statistics gathered in the United States show an increase for diagnosed males of 177% between 1980 and 2010, as opposed to an increase of 114% for females in the same time period, leading up to a ratio of 6.6% diagnosed men and 5.9% women, respectively, in 2014 [8]. Given that this study comprised a much higher ratio of men, more than two third of the studied group, it can be argued that cancer had a more significant impact in the sex distribution of the group. Digestive tract cancer types are proven to have a much higher prevalence in the male population than in the female one [9]. For example, in the United States, male colorectal cancer had an average annual incidence rate of almost 47 cases per 100.000 people, averaging 11 cases more than the female ratio. This evidence is supported also by the difference (between the sexes) of the incidence of liver, pancreas and stomach cancers, which is 7.8, 3.1 and 4.6 per 100.000 people, respectively [8]. Despite the small number of patients that this study had included, its results suggest the same global trends, with the number of male cancer diagnoses amounting to more than double that of the female cases (FERLAY & al. [10]).

Some pancreatic cancer statistics reveal that the average number of male cases per year is gradually higher than the female number until the age interval of 75 to 79 [11]. After this interval, the same studies show the exact opposite, with women having a higher incidence, peaking at a ratio of 2 over the age of 90. Overall, the cumulated average number of cases is highest starting with the age of 65. This study also showed the same ratios, with the number of patients diagnosed over the age of 65 being significantly higher than of other age groups.

Within the studied group, the majority of the patients did not have a family history of either digestive cancer or diabetes. However, those with a family history of any of the two had more aggressive types of cancer. Moreover, patients included in this category that were also diagnosed with metastatic cancer developed widely spread metastases, affecting multiple organs. Multiple global population studies argue that some diabetes drugs can be considered a risk factor for digestive tract cancers, but with inconclusive results (LI & al. [12]). This study also had inconclusive results in proving any relationship between the antidiabetic treatment and the aggressiveness of the diagnosed cancer. Diabetes did not deviate the distribution of cancer type in the studied group from the worldwide distribution of digestive cancers. As expected, the majority of patients were diagnosed with colorectal cancer, followed by pancreatic and gastric cancer.

Almost half of the patients comprised in this study were diagnosed with stage IV digestive tract cancers. In the case of colorectal cancers, which represented the majority of cancer cases, incidence by stage does not follow the patterns observed in international statistics [13]. It has been observed that these tumors were more aggressive, leading up to almost twofold the percentage of cases diagnosed with metastases at initial evaluation. On the other hand, the pancreatic cancer incidence indexed by stage was in line with international statistic results; 45% of the patients were diagnosed with stage IV tumors[14]. Gastric cases were mostly diagnosed in late stages. Furthermore, metastatic tumors were more frequently present in male patients than in female ones.

Correlations between cancer stadialization and inflammatory markers (LDH, ESR and CRP) had also been found. It was showed that advanced cases were corelated with elevated values of inflammatory markers while early stage cancers were not. From the studied group, in the case of the 16 patients who were diagnosed with metastases at the initial evaluation, 10 patients had elevated LDH levels (>2 times), 9 patients had raised ESR levels (>2 times) and 6 patients had raised CRP levels (>1 time).In the case of early stage cancer (stages 0,I and II) these indicators had normal values at diagnosis.

Endocan is a novel blood-and tissue-based biomarker. It is a product of endothelial cells, highly regulated by vascular endothelial growth factor and expressed during the switch between dormant to fast-growing angiogenic tumors studied in various types of cancer and inflammatory conditions. Multiple studies showed the bad prognosis signature of endocan biomarker in cancer (HUANG & al. [15]; BORCZUK & al. [16]; STANCIU & al. [17]).Sepsis and inflammation have associated endothelial dysfunction ranging from edema and vasodilation to ischemia and organ failure (DE FREITAS CAIRES& al. [18]; ARCAN & al. [19]; MIHAI & al. [20]). Since inflammatory mediators induce endocan expression, measured levels of this biomarker may closely reflect the severity of inflammation and of course the response to therapy (DE FREITAS CAIRES& al. [18]). It was shown that serum endocan levels are also increased in patients with inflammatory bowel disease (VOIOSU & al. [21]). Endocan may be a biomarker for both inflammatory disorders and tumor progression as well as a validated therapeutic target in cancer (SARRAZIN & al. [22]). More validation studies are however still required on larger cohorts on vascular endothelial growth factor-driven cancers. (MAZILU & al. [23]).

Conclusions

This study concludes that type II diabetes mellitus triggers a higher level of aggressivity in digestive tract cancers. The results have been confirmed by both paraclinical investigations and statistical results. Diabetes might also negatively impact the stage at diagnosis, as proven by the colorectal and gastric high incidence rates in advanced form. Thus, cancer screening is recommended for patients with type II diabetes and over 50 years old. In advanced stages, inflammatory markers were associated with tumor evolution and should be measured more frequently. The study also had inconclusive results in proving any relationship between the antidiabetic treatment and the aggressiveness of the diagnosed cancer.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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