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

NITIPIR CORNELIA [1,2]**, BARBU MARIA ALEXANDRA** [2]**, CRISTINA ORLOV**[2]**, ADINA ELENA STANCIU** [3,]**, POPA ANA MARIA** [2]**, RAZVAN HAINAROSIE**[4] **, SILVIU PITURU**[4]**, ANDREEALETITIA ARSENE**[6] **, ANCA PANTEA STOIAN**[5]

1.Carol Davila University, Medicine and Pharmacy Faculty, Medical Oncology Clinic
2. Elias Emergency University Hospital, Medical Oncology Department
3. Department of Carcinogenesis and Molecular Biology, Prof Dr Al Trestioreanu, Institute of Oncology Bucharest
4.Carol Davila University, Medicine and Pharmacy Faculty
5. Carol Davila University, Medicine and Pharmacy Faculty, Hygiene Departament,
6. Carol Davila University, Faculty of Pharmacy, Department of General and Pharmaceutical Microbiology

All authors had equal contribution to this research.
Corresponding authors:*Cristina Orlov e-mail:*orlov.cristina@gmail.com*, Ana-Maria Popa e-mail: amy.popa@yahoo.com*

Abstract

Introduction:
*   The number of digestive cancers cases has alarmingly increased within the past decades up to a current third placeranking 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 mellituswho 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 tumour 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.

Key words: diabetes, digestive cancers, risk factor, inflammatory syndrome

1.Introduction

The incidence of digestive cancers and diabetes has increased exponentiallyin the last decade. According to the International Diabetes Association, one out of 11 adults worldwide (415 million people) were diagnosed or were already suffering from diabetes (1).Of the many digestive tract

ORIGINAL PAPER

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 (3). Data shows that type 2 diabetes is strongly related to liver and pancreatic cancers (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 (4).Furthermore, some of the medications used for controlling diabetes have been shown to also have a negative link with certain types of cancer (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. (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 relevantfactors in determining either the relative risk of developing cancer or of the survival rate, for those already having a cancer-type condition (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. Thus, a chain of causality can be drawn starting from a diabetes condition that may lead to incidence or prognosis of cancers (6).

2.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 histopathologicalresults. All patients were initially evaluated byparaclinical(e.g. imagistic methods, such as computer tomography or magnetic resonance imaging - in selective patients), and by clinical findings(19).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.

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 later 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.

ORIGINAL PAPER

Table 1: Patient characteristics and diabetes treatment type

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

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

ORIGINAL PAPER

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

As previously mentioned, 16 patientswere 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	No patients	Percentage (%)
hepatic metastases	11	68.7
lymphatic metastases	7	43.7
pulmonary metastases	7	43.7
peritoneal metastases	5	31.2
bone metastases	4	25

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) elevatedlevelsof CEA and 4 had (>2 times) elevatedlevels while in the case of CA19-9 marker, 14 patients had (>3 times)raised levels and 2 patients had (>2 times) raisedlevels. 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 elevatedCRP levels (>1 time).

3.Results and discussion

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 (7). 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 (8). 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 4.6per 100.000 people, respectively (7). 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 (9).

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 (10). 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 patientsdidnot 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 (11). This study also had inconclusive results in proving any relationship between the antidiabetictreatment and the aggressiveness of the diagnosed cancer. Diabetes did not deviate the distribution ofcancer typein 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 (12). 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 (13). Gastric cases were mostly diagnosed in late stages.Furthermore, metastatic tumors were more frequently present in male patients than in female ones.

Corelations between cancer stadializationand inflammatory markers(LDH, ESR and CRP) had also been found in the results. It was showed that advanced cases were corelated with elevated values of inflammatory markerswhile early stagecancers 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 angiogenictumors studied in various types of cancer and inflammatory conditions.Multiple studiesshowedthe bad prognosis signature of endocan biomarkerin cancer (14,15).Sepsis and inflammation have associated endothelial dysfunction ranging from edema and vasodilation to ischemia and organ failure (16,20).Since inflammatory mediators induce endocanexpression, measured levels of this biomarker may closely reflect the severity of inflammation and of course the response to therapy (16).It was showed that serum endocan levels

Vol. , No. x,
Printed in Romania. All rights reserved
ORIGINAL PAPER

are also increased in patients with inflammatory bowel disease (17).Endocanmay be a biomarker for both inflammatory disorders and tumor progression as well as a validated therapeutic target in cancer (18).More validation studies are however still required on larger cohorts on vascular endothelial growth factor -driven cancers.

4.Conclusion

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 andover 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.

References

1. About Diabetes.International Diabetes Federation. N.p., 2017. Available from :http://www.idf.org/about-diabetes.Accessed 2017.01.05
2. Colorectal cancer statistics. Available from: http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/colorectal-cancer-statistics. Accessed 2017.01.10
3. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and Cancer: A consensus report. Diabetes Care. 2010;33(7):1674-1685. doi:10.2337/dc10-0666.
4. Vigneri P, Frasca F, Sciacca L, et al. Diabetes and cancer. Endocrine-Related Cancer .2009; 16:1103-1126. Doi:10.1677/ERC-09-0087.
5. Diabetes Medications and Cancer Risk: Review of the Literature Quang T. Nguyen, DO, FACE,* Lindsay Sanders, DO, MPH, Anu P. Michael, MD, Scott R. Anderson, MS IV, Loida D. Nguyen, PharmD, BCPS, and Zackary A. Johnson 2012 Jul; 5(4): 221–229.
6. D. Leroith, R. Novosyadlyy, E. J. Gallagher et al., "Obesity and Type 2 diabetes are associated with an increased risk of developing cancer and a worse prognosis; epidemiological and mechanistic evidence," Experimental and Clinical Endocrinology & Diabetes, vol. 116, supplement 1, pp. S4–S6, 2008. [4]. "Diagnosed Diabetes".
7. Cancer Facts & Statistics. (n.d.). American Cancer Society. Available from: https://cancerstatisticscenter.cancer.org/#/data-analysis/module/dw1qthUo/filter/site/Colorectum?type=barGraph. Accessed 2017.01.02
8. WHO - Burden: mortality, morbidity and risk factors – Cancer - Available from: http://www.who.int/nmh/publications/ncd_report_chapter1.pdf. Accessed 2017.01.10
9. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: http://globocan.iarc.fr Accessed on 2017.01.10
10. "Pancreatic Cancer Incidence Statistics." Cancer Research UK. N.p., 01 Dec. 2016. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/incidence#heading-One. Accessed 2017.01.06
11. Anti-diabetic therapies affect risk of pancreatic cancer Donghui Li, Sai-Ching J. Yeung, Manal M. Hassan, Marina Konopleva, James L. Abbruzzese 2009 Aug; 137(2): 482–488.
12. Colorectal Cancer Facts & Figures. Available from: http://www.cancer.org/research/cancer-facts-statistics/colorectal-cancer-facts-figures.html. Accessed on 2017.01.10

13. Statistics by cancer type. Cancer Research UK. Available from http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type. Accessed 2017.01.02

14. Huang GW, Tao YM, Ding X (2009) Endocan expression correlated with poor survival in human hepatocellular carcinoma. Dig Dis Sci 54: 389-394. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18592377. Accessed on 2017.01.10

15. Borczuk AC, Shah L, Pearson GD, Walter KL, Wang L, et al. (2004) Molecular signatures in biopsy specimens of lung cancer. Am J RespirCrit Care Med 170: 167-174. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15087295. Accessed on 2017.01.10

16. De Freitas Caires N, Legendre B, Parmentier E, Scherpereel A, Tsicopoulos A, Mathieu D, et al. Identification of a 14 kDaendocan fragment generated by cathepsin G, a novel circulating biomarker in patients with sepsis. (45-51).J Pharm Biomed Anal. 2013:78–79. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23454598. Accessed on 2017.01.14

17. Serum endocan levels are increased in patients with inflammatory bowel disease. Voiosu T, Bălănescu P, Benguş A, Voiosu A, Baicuş CR, Barbu M, Ladaru A, Nitipir C, Mateescu B, Diculescu M, Voiosu R. Clin Lab. 2014;60(3):505-10. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24697130. Accessed on 2017.01.14

18. Endocan or endothelial cell specific molecule-1 (ESM-1): a potential novel endothelial cell marker and a new target for cancer therapy. Sarrazin S1, Adam E, Lyon M, Depontieu F, Motte V, Landolfi C, Lortat-Jacob H, Bechard D, Lassalle P, Delehedde M. BiochimBiophysActa. 2006 Jan;1765(1):25-37. Epub 2005 Aug 26. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16168566. Accessed on 2017.01.14

19. Mihai D , Brătilă E , Mehedinţu C , Berceanu C , Piţuru SM, The ethical aspects   regarding cryopreserved embryos, Romanian Journal Of Legal Medicine, 2017 25: 3:317-321

20. Arcan, Oana; Bild, Walther; Ciobica, Alin; et al., Angiotensin-(1-7) intracerebroventricular administration generates nociceptive effects in hot-plate task and decreased oxidative stress in the temporal lobe, ROMANIAN BIOTECHNOLOGICAL LETTERS Volume: 19 Issue: 5 Pages: 9763-9771 Published: SEP-OCT 2014