https://doi.org/10.46389/rjd-2021-1007
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2021; volume 28, issue 1, pages 47-53

Original Research

Colorectal cancer in patients with diabetes mellitus

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Received: 31 December 2020 / Accepted: 8 March 2021

Abstract

Background and Aims: Diabetes mellitus (DM) and colorectal cancer are two common diseases, with a growing trend and the major causes of mortality and morbidity, with a negative impact on life expectancy and quality of life, with socio-economic impact, which makes them a major public health problem. DM is the etiopathogenic factor involved in several diseases, including cancer. There are numerous studies on DM as a risk factor for breast, endometrial, pancreatic, liver cancer, non-Hodgkin's lymphoma, but also colorectal cancer. **Material and Method:** The study includes patients hospitalized in the Gastroenterology Department for digestive symptoms who after a colonoscopic and bioptic examination were diagnosed with colon/rectal adenocarcinoma and who were subsequently hospitalized in the General Surgery Department for surgery. Patients were divided into two groups: with and without diabetes mellitus. All patients in the study followed the same oncological protocol and were monitored dynamically at 3-6-9-12 months after diagnosis. **Results:** Diabetic patients were frequently associated with obesity and a more advanced stage of the oncological disease (DM – stage I:20%, stage II: 24%, stage III: 36%, stage IV: 20%; non-DM – stage I: 23%, stage II 28.2%, stage III: 34.7%, stage IV: 14.1%). No major differences were observed among diabetic patients regarding the type of antidiabetic treatment and the stage of the disease. Postoperative complications were more common in diabetic patients (24%), and the survival rate was slightly lower among patients with DM (80%). **Conclusions:** The long-term survival of colorectal cancer patients who have received surgical treatment depends on the stage of the disease, the patient's age, and the associated pathologies. DM brings additional contributions to oncological risk, being a risk factor for the oncological process in general and for colorectal cancer in particular.

Keywords: Colorectal cancer, connection, diabet mellitus, follow-up.

Background and Aims

Diabetes mellitus (DM) and colorectal cancer (CRC) are diseases with an increasing impact on the population; DM representing the disease of the century with a global prevalence that has doubled since 1980, increasing from 4.7–8.5 in the adult population. type 2 DM accounts for 90–95% of all cases of DM worldwide, totaling about 191 millions, in 2002 [1, 2]. In an important measure, but of a smaller magnitude, the prevalence of CRC is on the rise, being the third most common cancer and the second most common cause of cancer mortality at the global level [3].

Epidemiological studies suggest a link between type 2 DM and CRC. People with DM have a higher risk of developing cancer and at the same time have a higher mortality rate [4]. DM and CRC have in common a number of general

risk factors prevalent in populations where a Western lifestyle is prevalent (diet high in animal fats and poor in vegetables/fruits, high consumption of red meat, refined carbohydrates; sedentary lifestyle, obesity) [5]. Obesity and diabetes are epidemiologically associated with cancer risk, and both together, but also separately, are demonstrated risk factors for cancer in general and for CRC in particular [6, 7].

The number of deaths from DM and CRC has increased by up to 90%and 57%, respectively, in the last 20 years at the global level [1]. The risk of developing CRC in diabetic patients was estimated to be 27% higher than in non-DM patients [8]. Early detection of DM and CRC substantially increases the chances of treatment and survival. More than a third of deaths from CRC could be prevented by a rigorous screening program for people at high risk for cancer. Strategies to promote the prevention and early detection of these diseases are urgently needed [9].

Material and Method

This study refers to patients admitted to the Gastroenterology Department of the Emergency Hospital of Constanta, who underwent a colonoscopic and bioptic examination and were diagnosed with CRC and who needed hospitalization in the Department of General Surgery in order to perform surgery, during January 2017–2019. For 103 of the patients, the biopsy showed colonic or rectal adenocarcinoma; 25 of these patients had associated DM.

Patients were hospitalized in the GastroeterologyDepartment for digestive symptoms (transit disorders: constipation/diarrhea, abdominal pain, rectorage), with or without alteration of the general condition (fatigue, marked weight loss, anemia). As landmarks we evaluated the following: age, gender, body mass index (BMI), smoker status, alcohol consumption, type of patient's diet, first symptom. In patients with DM, we also evaluated: the duration of the disease, the type of treatment (insulin or oral antidiabetics drugs: OADs), the duration of treatment, the complications caused by the disease. From a biological point of view, we evaluated: blood glucose value, glycosylated hemoglobin, tumor markers (CEA, CA 19-9).

All patients in the study had as recommendations: oncological and surgical consultation, complementary imaging explorations for staging. The patients were followed in dynamics, and after the surgery, visits were performed at 3-6-9-12 months, establishing the stage of the disease, the type of oncological treatment, the survival rate. Of the 103 patients enrolled in the study, patients were divided into two groups: with DM and non-DM.

Results

Between January 2017–2019, 103 patients were diagnosed with colon or rectal adenocarcinoma, with histopathological confirmation. Patients were divided into two groups: with DM (25) and non-DM (78). In both groups the sex ratio was inclined in favor of men, the median age of those associated with DM (68) was higher compared with those non-DM (66.5). Most DM patients come from rural areas (60%), a possible fact for the delayed presentation to the doctor, for the deficient control of DM; the patients being in an area considered as disadvantaged of the country. The most common first symptom in the group with DM was abdominal pain (44%), followed by transit disorders (24%); conversely compared to non-DM patients (abdominal pain: 29.48%, intestinal transit disorders: 44.87%). Abdominal discomfort and abdominal pain usually occur in a more advanced stage of the disease, initially appearing changes in bowels habits (like: frequencies, color, shape, constipation or diarrhea) that send the patient to the doctor in time [10].

In both groups most of the patients developed colon adenocarcinoma (DM: 80%, non-DM: 73.07%) and in 20% of the cases, they developed rectal adenocarcinoma. There were also patients who had previously other cancers, such as breast, stomach, prostate, lung cancer, but also patients with metachronous cancer (DM: 8%, non-DM: 3.84%). Six of the non-DM patients had a family history of CRC. Diabetic patients associated: obesity (median BMI = 30.02 kg/m^2), compared to

https://doi.org/10.46389/rjd-2021-1007

Table 1: Clinical data of the patients with or without DM.

		DM	Non-DM	Total
Overall (no, %)		25 (24.27%)	78 (75.73%)	103(100%)
Gender	Men	16(64%)	41(52.56%)	57(55.34%)
	Women	9(36%)	37(47.44%)	46(44.66%)
Age (years, median)		51–85 (68)	38–86 (66.5)	36–86 (67)
Environment	Urban	10 (40%)	58 (74.35%)	68 (66.01%)
	Rural	15 (60%)	20 (25.65%)	35 (33.99%)
The first symptom	Abdominal pain	11 (44%)	23 (29.48%)	34 (33.01%)
	Intestinal transit disorders	6 (24%)	35 (44.87%)	41 (39.8%)
	Rectal hemorrhage	5 (20%)	13 (16.66%)	18 (17.47%)
	Anemia	1 (4%)	3 (3.84%)	4 (3.88%)
	Weight loss	2 (8%)	4 (5.12%)	6 (5.82%)
Colon cancer		20 (80%)	57 (73.07%)	77 (74.75%)
Rectal cancer		5 (20%)	21 (26.93%)	26 (25.25%)
Other cancers	Metachronous	2 (8%)	3 (3.84%)	5 (4.85%)
	Breast	0	4 (5.12%)	4 (3.88%)
	Prostate	1 (4%)	3 (3.84%)	4 (3.88%)
	Pulmonary	0	1 (1.28%)	1 (0.97%)
	Gastric	0	1 (1.28%)	1 (0.97%)
	Another location	0	0	0
Family history of cancer		0	6 (7.69%)	6 (5.82%)
BMI (kg/m^2), median		21.91–49.67 (30.02)	17.3–39.84 (25.49)	17.03–49.67 (27.04)
Hypertension		19 (76%)	11 (14.1%)	30 (29.12%)
Smokers		7 (28%)	12 (15.36%)	19 (18.44%)
Alcohol consumers		4 (16%)	7 (8.97%)	11 (10.67%)

25.49 kg/m^2 in non-DM patients), hypertension (DM: 76%, non-DM: 14.1%) and higher tobacco use (>10 cigarettes/day, >10 years) and alcohol (high consumption) (Table 1).

All patients with DM had type II, 68% being treated with OADs (with a median time of 7 years) and 32% with insulin (with a median time of 11 years). From personal history we found that 20% of patients suffered from diabetic neuropathy, 12% from diabetic nephropathy and 4% from diabetic angiopathy (Table 2).

All patients diagnosed with rectal adenocarcinoma received preoperative radiotherapy and neoadjuvant chemotherapy. All patients underwent surgery. Postoperative complications were more common in patients with DM, who had a slower cure (24%) than in non-MD patients (5.12%). Regarding staging, diabetic patients were diagnosed in an advanced stage of the disease. Postoperatively, no patient received radiotherapy, according to the protocol 68% of diabetics received chemotherapy and 62.83% of non-MD. (Table 3.)

After the surgery, the patients were followed at 3-6-9-12 months by medical visits or by telephone, when: their general condition, paraclinical examinations performed postoperatively in dynamics (tumor markers, computed

tomography), and the appearance of possible complications/secondary determinations was evaluated. Survival at 1 year is higher in the group of non-DM patients (85%) than in patients with DM (80%) (figure 1).

Table 2: Characteristics of patients with DM and CRC.

Patients with DM And CRC		
The type of diabetes	Type 1	0
	Type 2	25
The type of treatment	No treatment	0
	OADs	17 (68%)
	Insulin	8 (32%)
Duration of disease	No treatment	0
	OADs (years, median)	1–15 (7)
	Insulin (years, median)	2–30 (11)
Complications	Diabetic angiopathy	1 (4%)
	Diabetic retinopathy	2 (8%)
	Diabetic neuropathy	5 (20%)
	Diabetic nephropathy	3 (12%)
	Skin infections	1 (4%)
	Without complications	13 (52%)

Discussion

A 2010 report by the American Diabetes Association recognizes the link between DM and CRC [11]. Patients with DM have a 30% higher risk of developing CRC compared to non-DM patients, with similar results for both sexes [8]. Risk factors such as obesity, tobacco use and alcohol are involved in the development of DM and CRC. Overweight and obese patients have a higher risk of developing DM. Studies have shown that DM and obesity are proven risk factors for cancer in general and for CRC in particular. Obesity control through measures to prevent/reduce overweight can become a relevant method in reducing the risk of developing DM and implicitly CRC [12–15].

Cancer shares with obesity and DM a common metabolic and humoral environment (proinflammatory cytokines, hyperinsulinism, elevated serum IGF-1 levels). Obesity and DM are often associated, but the overlap is not perfect. Current epidemiological data show that DM is associated with most obesity-related cancers, but the link is much closer to DM, suggesting that DM makes additional contributions to cancer risk

Table 3: Pre/postoperative staging and treatment management in patients with/without DM.

	DM	NON-DM	TOTAL
Overall (no, %)	25 (24.27%)	78 (75.73%)	103 (100%)
Neoadjuvant oncological treatment			
Without treatment	20 (80%)	57 (73.07%)	77 (74.75%)
Chemotherapy	5 (20%)	21 (26.93%)	26 (25.25%)
Radiotherapy	5 (20%)	21 (26.93%)	26 (25.25%)
Surgical treatment			
Yes	25 (100%)	78 (100%)	103 (100%)
No	0	0	0
Postoperative complications			
Wound infection	2 (8%)	4 (5.12%)	6 (5.82%)
Pneumonia	1 (4%)	1 (1.28%)	2 (1.94%)
Hydroelectrolyte imbalance	2 (8%)	3 (3.84%)	5 (4.85%)
Slow healing	6 (24%)	4 (5.12%)	10 (9.7%)
Staging			
Stage I	5 (20%)	18 (23%)	23 (22.33%)
Stage II	6 (24%)	22 (28.2%)	28 (27.18%)
Stage III	9 (36 %)	27 (34.7%)	36 (34.95%)
Stage IV	5 (20%)	11 (14.1%)	16 (15.53%)
Adjuvant oncological treatment			
Without treatment	8 (32%)	29 (37.17%)	37 (35.92%)
Chemotherapy	17 (68%)	49 (62.83%)	66 (64.08%)
Radiotherapy	0	0	0

https://doi.org/10.46389/rjd-2021-1007

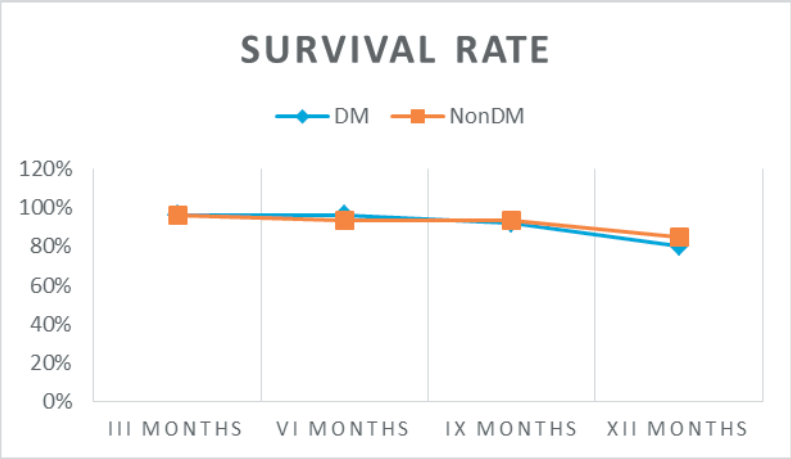

Figure 1: Survival rate in DM patients compared to non-DM patients in the first year of surveillance.

[16]. In our study, DM patients also had associated obesity, median BMI: 30.02 kg/m^2.

Other risk factors for DM and CRC are tobacco and alcohol consumption. There are prospective studies that have shown that smoking is a risk factor in the development of DM [17]. Tobacco use also increases the risk of developing adenomatous polyps that are precursors of CRC lesions and in current studies is considered to be a risk factor for CRC [18]. Intense alcohol consumption has been associated with an increased risk of developing DM and also increases the risk of developing CRC [19, 20]. Tobacco and alcohol consumption is also found in patients in our study (28% smokers, 16% alcohol users) in diabetic patients, in a much higher percentage than non-DM (15.36% smokers, 8.97% alcohol users).

An additional hypothesis to explain the association between DM and CRC is slowed intestinal transit, a common complication in diabetics due to diabetic neuropathy (which causes elevated concentrations of secondary bile acids in the stool with carcinogenic potential) and which is associated with elevated blood glucose levels and triglycerides. Although this explanation is not prevalent in the pathophysiological explanations of CRC, its scientific relevance is supported by data from the literature, demonstrating on an animal model that fecal bile acids can lead to CRC [21–23].

From a biological point of view, a relationship between DM and CRC can be established. Patients with type II DM in the early stages of the disease are characterized by elevated insulin concentrations, which have also been associated with colorectal cancerogenesis. Endogenous hyperinsulinemia, which occurs in the early stages of diabetes as a compensatory phenomenon for peripheral insulin resistance, develops after frequent exposure of obese patients to elevated circulating levels of glucose and lipids. How insulin produces intracellular signals differs between individuals with DM and healthy individuals; insulin resistance causes metabolic signaling to be altered while maintaining and increasing proliferative signals. Thus, excess endogenous insulin in DM patients by amplifying antiapoptotic and pro-mitogenic signals may initiate or maintain an oncogenic process [24].

The mechanisms of oncogenesis, from the existing data in the literature, involve several levels: hyperglycemia may promote pathogenic mechanisms, and there is a recent link between hyperglycemia and increased incidence of CRC (but also gastric and endometrial cancer) and mortality from CRC. All these data must be looked at with caution because beyond a plausible biological point of view, is the fact that oncogenesis in CRC involves a long period of action of risk factors [24, 25].

The treatment of patients with DM consists of a wide range of drugs; often a patient may change their dose or type of medication over the years or receive more than one medication at a time. The potential role of these drugs in favor of cancer is unclear, but most likely is minor, if exists [26, 27].

Considering that the appearance of CRC is preceded by a long period of exposure to carcinogenic risk factors (20–30 years), the duration of insulin treatment was studied as an important contributor to the role of insulin risk factor and it was concluded that there is a higher risk of developing CRC within 5 years of diagnosing DM. Also, by comparing patients with insulin treatment to those without insulin, a double increase in the risk of CRC can be observed in the first category [28–30]. Most diabetic patients in our study received treatment with OADs (68%) and had a median time of treatment of seven years. Patients treated with insulin had a median time of 11 years, so the treatment of patients with DM may be an associated risk factor for CRC.

Considering that DM is an underdiagnosed disease, when it comes to the time of exposure of patients to DM, confusion can occur. Many patients are diagnosed at the onset of symptoms, not after screening. Regarding oncological treatment in patients with DM and CRC, there is no evidence to support specific approaches to chemotherapy and no benefits have been observed during survival [31]. Patients in stages II and III who received adjuvant chemotherapy and associated DM had a higher recurrence and a higher mortality rate than patients without diabetes [32]. Thus, short- and long-term mortality in patients combining CRC and DM is higher than in patients with CRC and non-DM. The data from our study are similar to the literature, comparing the survival of DM patients with those without DM, the 1-year survival rate being 80% in DM patients and 85% in non-DM patients.

Conclusions

DM is a risk factor for CRC involved in both the early and the advanced stages of oncogenesis, but more than that it is also an important prognostic factor. National guidelines do not include DM as a risk factor for screening for CRC, although the increased risk for colorectal adenomas in DM patients is similar to the risk of personal history of colorectal adenomas or the risk associated with the presence of a first-degree relative with CRC. We consider that colonoscopic screening in patients with DM is required as a major part of the measures aimed at decreasing the prevalence of CRC. The wide recognition in the medical world of the connection between the two sufferings with increasing prevalence is a necessary premise for the containment of the phenomenon at a global level.

Conflict of Interest

The authors declare no conflict of interest.

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