# Influence of type II diabetes mellitus on postoperative complications following colorectal cancer surgery

RĂZVAN CĂTĂLIN POPESCU[1,2], NICOLETA LEOPA[1,2], EUGEN DUMITRU[2,3], ANCA FLORENTINA MITROI[4], CRISTINA TOCIA[2,3], ANDREI DUMITRU[2,3], COSTEL BRÎNZAN[4] and FLORIN BOTEA[5]

[1]Department of General Surgery, Emergency Hospital of Constanța, 900591 Constanța; [2]Faculty of Medicine and Pharmacy Constanta, Ovidius University, 900470 Constanța; Departments of [3]Gastroenterology and [4]Pathology, Emergency Hospital of Constanța, 900591 Constanța; [5]Dan Setlacec Center of General Surgery and Liver Transplantation, Fundeni Clinical Institute, 022328 Bucharest, Romania

**Abstract.** Diabetes mellitus (DM) promotes colorectal cancer (CRC) carcinogenesis through complex processes and is considered as an independent risk factor for cancer in general and for CRC in particular. Diabetic patients have complications in the postoperative period following CRC surgery. The aim of the present study was to explore the effect of type II DM (T2DM) on postoperative outcomes for CRC compared with non-diabetic patients. The present study analyzed the data from patients admitted to the General Surgery Department, Emergency Hospital of Constanța (Romania) diagnosed with CRC and DM compared with a control group (patients with CRC, without DM, recruited in the same period and frequency matched to cases by number, sex and age) analyzing patient comorbidities and postoperative complications. A total of 61 patients had undergone surgery for CRC and met the inclusion criteria in the present study conducted during September 2020-2021. A total of 30 patients associated T2DM. Diabetic patients have been associated with more comorbidities than non-diabetics; the age-adjusted Charlson comorbidity index score ≥6 was identified in 90% of diabetic patients compared with 45.2% of controls. Grade III Clavien-Dindo classification was observed in 13.3% diabetic patients compared with 3.2% of non-diabetic patients. Additionally, a higher rate of urinary and pulmonary complications (6.7 vs. 3.2% in controls respectively) in patients with diabetes was found. Postoperative hospitalization was prolonged in diabetic patients (P=0.042). Univariate and multivariate analyses revealed that the laparoscopic approach for diabetic patients was found to be associated with <grade III Clavien-Dindo classification (P=0.040) and the absence of surgical site infection (P=0.040). Diabetes predisposes patients to numerous postoperative complications following CRC surgery and postoperative therapeutic conduct must be personalized to prevent possible postoperative complications following CRC.

## Introduction

Colorectal cancer (CRC) is a malignancy with several possible risk factors such as diabetes, obesity, a diet rich in red meat, constipation and inflammatory bowel diseases and is the second most common cause of cancer-related mortality worldwide (1). Diabetes mellitus (DM) is a leading cause of global deaths with an increasing incidence rate, rendering it a serious public health concern (2). In 2017, 451 million people were diagnosed with diabetes worldwide and the prevalence in the next 25 years is expected to increase by >200 million new cases (2). Type II DM (T2DM) accounts for approximately 90 to 95% of all diagnosed cases of diabetes and has a similar global trend to that of total diabetes (3), with developing countries exhibiting an increase in the number of newly diagnosed cases (4,5).

Increased mortality from cancer, cardiovascular disease, kidney disease, stroke or infection has been associated with diabetes in a number of studies (6,7). DM promotes CRC carcinogenesis through complex processes and is considered an independent risk factor for cancer in general and CRC in particular (8). Postoperative complications lead to an increase in the mortality rate of patients with DM compared with those without (30-40% higher risk) (8).

It is known that ~20% of surgical patients have DM and ~50% of those patients with DM require surgery at some point in their lives (9). In patients with DM, postoperative outcomes may be influenced by micro- and macrovascular pathology that, in combination with the inherent higher risk of CRC surgery itself and older age, may have a particularly negative effect on patients (10,11). Infection-related hyperglycemia is a recognized underlying factor that mediates poor DM outcomes and studies have also reported an association with thrombosis by endothelial cell dysfunction as an action of inflammatory markers and oxidative stress (9,12).

*Correspondence to:* Dr Nicoleta Leopa, Department of General Surgery, Emergency Hospital of Constanța, 145 Tomis Boulevard, 900591 Constanța, Romania
E-mail: gherghe_nicoleta02@yahoo.com

The aim of the present study was to determine the effect of T2DM on the postoperative outcomes in patients undergoing CRC surgery and to highlight whether the presence of diabetes has exacerbated the disease or the immediate postoperative mortality.

**Materials and methods**

*Study group.* A case-control study was conducted among adult South-Eastern Romanian patients diagnosed with CRC and T2DM, prospectively admitted for elective surgery to the Department of General Surgery, Emergency Hospital of Constanța (Constanța, Romania) between September 2020 and September 2021. The patients had positive colonoscopy results for a malignancy, and histologically confirmed this as CRC. The inclusion criteria were as follows: i) Patients diagnosed with CRC; ii) elective cases; iii) patients with T2DM. The exclusion criteria were as follows: i) Non-elective surgery for CRC (patients with a complication of a colorectal tumor, including stenosis, perforation and hemorrhage, without histopathological diagnosis of malignancy); ii) previous history of cancer; iii) familial history of CRC. Control subjects included patients with CRC without DM who were recruited in the same period and were frequency-matched to cases on number, sex and age. Of the 103 patients prospectively admitted to the Department of General Surgery, 61 patients met the inclusion and exclusion criteria and were enrolled in the study; the clinicopathological characteristics of the patients are listed in Table I.

According to the WHO criteria, T2DM is characterized by an inability of the body to produce insulin properly and a plasma glucose concentration of ≥7.0 mmol/l (13). Age-adjusted Charlson comorbidity index (ACCI) score was calculated based on the comorbidities and the age of the patients (14). Postoperative complications were assessed and categorized using the Clavien-Dindo classification (15). The Clavien-Dindo classification was used to categorize postoperative complications; complications of grade IIIA and above were considered major complications (15). Short-term complications were defined as complications occurring within 30 days and included surgical site infection (SSI), anastomotic leakage (AL), ileus, intra-abdominal abscess, mechanical wounds or pulmonary/cardiac/urinary complications. Postoperative mortality was defined as succumbing within 3 months of surgery.

CRC lesions were treated using laparoscopy or open surgery. The pathological stage, size and localization of the tumor were recorded. Demographic and clinical data included age, sex, alcohol consumption and smoking status [according to the National Institute on Alcohol Abuse and Alcoholism (16) and the Center for Disease Control and Prevention (17)] of participants were recorded and the body mass index (BMI) was calculated.

*Ethical approval.* The present study was approved by the Local Ethics Commission for the Approval of Clinical and Research Developmental Studies, County Clinical Emergency Hospital of Constanța, in accordance with the Declaration of Helsinki on experimentation with human subjects. Informed consent was obtained from all patients at the time of enrolment (approval no. 12/2020).

*Statistical analysis.* SPSS version 18 (SPSS, Inc.) was used for statistical analysis. Results are presented as a mean ± standard deviation, with categorical variables expressed as counts. For comparison between variables, the Mann Whitney U-test was used for continuous variables and the $\chi^2$ test or Fisher exact test (when cell count was zero) were used for categorical variables. Univariate and multivariate binary logistic regression models were used to determine the independent risk factors for CRC adjusted for age, BMI, smoking and alcohol consumption status. Odds ratios and 95% CIs were estimated. P<0.05 was considered to indicate a statistically significant difference.

**Results**

The demographics and clinicopathological characteristics of patients included in the study are provided in Table I. Patients with T2DM were age-matched (within 5 years) with control participants; the mean age was 69.90 years for T2DM patients and 66.1 years for control patients. There were no statistically significant differences identified in the mean age, sex, smoking status and habitual alcohol drinker status. A significant difference in glucose level (P<0.001), hemoglobin (Hb)A1c (P<0.001), carbohydrate antigen (CA)19-9 (P=0.015) and BMI (P=0.023) was observed between the two groups. However, the ACCI score was higher in patients with T2DM compared with controls (P=0.004).

Postoperative complications in patients with CRC with and without diabetes are presented in Table II. The occurrence of postoperative complications was significantly lower in patients without T2DM compared with patients with DM (P=0.046). The major complication rate among T2DM patients was 13.3% (n=4); these patients all had grade III Clavien-Dindo and the complications were as follows: Anastomotic leakage with intraperitoneal abscess requiring reintervention (n=1), SSI requiring percutaneous drainage (n=1), surgical debridement and appropriate systemic antibiotic therapy (n=2). In patients without T2DM, one case had an SSI that required debridement under local anesthesia. The minor complication rate was 16.7% (n=5) for patients with T2DM; these patients were grade II (no patients were grade I) and the complications were as follows: Delayed gastric emptying (n=1; treated by medication and nasogastric tube); postoperative lymphatic leakage (n=2; treated with medication), intra-abdominal hemorrhage (n=1; requiring blood transfusion) and wound infection (n=1; treated with antibiotics). Control patients exhibited a minor complication rate of 6.5%; the patients were classified as Clavien-Dindo grade I (n=1; wound bleeding, treated conservatively) and grade II (n=1; delayed gastric emptying, treated by nasogastric tube and medication). In addition, a higher rate of urinary and pulmonary complications was observed in patients with T2DM (6.7 vs. 3.2% in controls respectively). Postoperative hospitalization was longer in patients with T2DM compared with those without T2DM (P=0.042) and no postoperative 30-day mortality rate or readmission were observed.

The histopathological characteristics of the tumors and the TNM stage were not influenced by the presence of diabetes

Table I. Baseline demographics, comorbidity and surgical procedure of the patients.

| | CRC cases (n=61) | | |
| Variable | T2DM (n=30) | No T2DM (n=31) | P-value |
|---|---|---|---|
| Age, years[a] | 69.90±8.36 | 66.10±11.69 | 0.139 |
| Sex, n (%) | | | 0.869 |
|   Male | 19 (63.3) | 19 (61.3) | |
|   Female | 11 (36.7) | 12 (38.7) | |
| Smoker[b], n (%) | 9 (30) | 7 (22.6) | 0.510 |
| Habitual alcohol use[c], n (%) | 6 (20) | 2 (6.5) | 0.110 |
| BMI, kg/m²[a] | 30.75±3.90 | 28.61±4.65 | 0.023 |
| HbA1c[a] | 6.86±0.73 | 5.01±0.39 | <0.001 |
| Glu, mg/dl[a] | 143.29±14.59 | 87.06±9.40 | <0.001 |
| CEA, ng/ml[a] | 102.90±49.66 | 105.92±48.24 | 0.710 |
| CA19-9, U/ml[a] | 106.78±39.75 | 286.39±50.35 | 0.015 |
| ACCI[a] | 7±1.48 | 5.06±1.63 | 0.004 |
|   0-1, n (%) | 0 (0) | 0 (0) | |
|   2-3, n (%) | 0 (0) | 6 (19.6) | |
|   4-5, n (%) | 3 (10) | 11 (35.5) | |
|   ≥6, n (%) | 27 (90) | 14 (45.2) | |
| Surgical approach | | | 0.457 |
|   Laparoscopy | 8 (26.7) | | |
|   Open | 22 (73.3) | | |
| Operation time, min[a] | 191.83±20.78 | 196.15±25.67 | 0.013 |

[a]Mean ± standard deviation. [b]Smoker was defined as smoking of ≥10 cigarettes daily. [c]Alcohol consumption was defined as ≥1 drink per day for women and ≥2 drinks per day for men. ACCI, age-adjusted Charlson comorbidity index; BMI, body mass index; CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; CRC, colorectal cancer; Glu, glucose; HbA1c, hemoglobin A1c; T2DM, type II diabetes mellitus.

(Table III). The most common location of tumors was the left colon in T2DM patients and the rectum in non-diabetic patients.

Univariate and multivariate analysis of the type of surgical approach was performed in patients with T2DM and CRC and is presented in Table IV. Among the various parameters studied, the presence of ileus (P=0.008) was found to be significant during univariate analysis for laparoscopic surgery. Multivariate analysis revealed that the laparoscopic approach was associated with ≥grade 3 and below in the Clavien-Dindo classification (P=0.040) and with the absence of an SSI (P=0.040). The number of lymph nodes retrieved in the specimen did not differ depending on the approach (laparoscopy 18.63±8.94 vs. open 16±6.34), but the number of days of postoperative hospitalization did differ (laparoscopy 6.63±0.91 vs. open 7.64±2.46); however, neither of these were found to be significantly different.

**Discussion**

Patients with DM have a higher risk of postoperative complications and mortality following colorectal surgery (18,19). The results of the present study showed that patients with diabetes had a higher rate of postoperative complications compared with non-diabetic patients. Among the common postoperative complications encountered in surgical patients, SSI has been the focus of medical attention (20). The present study found SSI to be the most commonly reported postoperative complication amongst patients with T2DM, the data being similar to those previously reported.

Lin et al (21) were the first to provide strong evidence that diabetes is independently and significantly associated with an increased risk of AL mortality in CRC surgery. Only one patient with AL was identified in the present study, who also developed an intraperitoneal abscess and who had late manifestations and symptoms, requiring reintervention, with a favorable outcome thereafter.

High levels of preoperative blood glucose and HbA1c may be an indicator of postoperative infection in patients with gastrointestinal disorders, including CRC, but this is still disputed in the literature (22). In the present study, preoperative HbA1c levels did not predict postoperative outcomes, such as ileus or wound infection. Postoperative ileus was attributed to myenteric neuron damage from chronic DM, which is a common cause of diabetes-associated gastrointestinal complications (23). Ileus was identified in more patients in the T2DM group (n=7) compared with the non-DM group (n=2), and additional prokinetic drugs were administered to those patients.

Diabetes is a predisposing factor for developing postoperative urinary and pulmonary complications (24). In the present

Table II. Postoperative outcomes of patients CRC with or without T2DM.

| Variable | CRC cases (n=61) | | OR (95%CI) | P-value |
|---|---|---|---|---|
| | T2DM; n=30 (%) | No T2DM; n=31 (%) | | |
| Any postoperative complication | 9 (30) | 3 (9.7) | 0.250 (0.060-1.038) | 0.046 |
| Clavien-Dindo classification | | | | |
|   Grade I | 0 (0) | 1 (3.2) | 1.033 (0.969-1.102) | 0.242 |
|   Grade II | 5 (16.7) | 1 (3.2) | 0.167 (0.018-1.522) | 0.078 |
|   Grade IIIA | 3 (10) | 1 (3.2) | 0.300 (0.029-3.059) | 0.285 |
|   Grade IIIB | 1 (3.3) | 0 (0) | 0.967 (0.905-1.033) | 0.305 |
|   Grade IVA | 0 (0) | 0 (0) | - | ns |
|   Grade IVB | 0 (0) | 0 (0) | - | ns |
|   Grade V | 0 (0) | 0 (0) | - | ns |
| Reoperation | 1 (3.3) | 0 (0) | 0.967 (0.905-1.033) | 0.305 |
| Anastomotic leakage | 1 (3.3) | 0 (0) | 0.967 (0.905-1.033) | 0.305 |
| Infectious complications | | | | |
|   Surgical site infection | 3 (10) | 1 (3.2) | 0.300 (0.029-3.059) | 0.285 |
|   Intra-abdominal abscess | 1 (3.3) | 0 (0) | 0.967 (0.905-1.033) | 0.305 |
|   Septicemia | 0 (0) | 0 (0) | - | ns |
| Systemic complications | | | | |
|   Urinary complications | 2 (6.7) | 1 (3.2) | 0.467 (0.40-5.435) | 0.531 |
|   Pulmonary complications | 2 (6.7) | 1 (3.2) | 0.467 (0.40-5.435) | 0.531 |
|   Cardiac complications | 0 (0) | 1 (3.2) | 1.033 (0.969-1.102) | 0.242 |
| Mechanical failure of wound healing | 2 (6.7) | 0 (0) | 0.933 (0.848-1.027) | 0.088 |
| Ileus | 7 (23.3) | 2 (6.5) | 0.227 (0.043-1.197) | 0.057 |
| *Clostridium difficile* colitis | 1 (3.3) | 0 (0) | 0.967 (0.905-1.033) | 0.305 |
| Postoperative hospital stay[a] | 7.03±1.21 | 6.13±0.88 | - | 0.042 |
| 30-day mortality | 0 (0) | 0 (0) | - | ns |
| Readmission | 0 (0) | 0 (0) | - | ns |

[a]Mean ± standard deviation. CI, confidence interval; CRC, colorectal cancer; ns, not significant; OR, odds ratio; T2DM, type II diabetes mellitus.

study, the rate of pulmonary and urinary complications was lower in control patients compared with patients with diabetes; but the rate were not significantly different.

Minimally invasive surgery has several benefits, including reduced postoperative complications and a link with early mobilization and a reduced occurrence of ileus, opiate requirements and pain; it should therefore be considered for patients with diabetes (25,26). Laparoscopically resolved CRC cases were more common in patients without diabetes, with surgery being slightly longer, but with lower comorbidities. In the group of patients with diabetes, univariate and multivariate analysis revealed that laparoscopic surgery is significantly beneficial, owing to the decreased number of postoperative complications associated with a reduced hospital stay.

The therapeutic management of diabetic patients who develop CRC should be carefully studied in terms of the dosing of pre-operative antidiabetic medication, the most suitable approach and strict glycemic control immediately following surgery. The administration of insulin in patients with hyperglycemia and elevated risk of infectious complications improves postoperative infections (27).

The present study was a step towards obtaining an improved understanding of possible complications following CRC surgery, particularly complications that may occur in patients with diabetes. The present study did not consider the presentation of the link between diabetes and CRC from a genetic point of view, this being the subject of a future article. Being aware of the potential complications can lead to the development of means to prevent them. For diabetic patients, laparoscopic surgery and decreasing septic operative time (performing mechanical anastomoses) are recommended, and postoperative therapeutic management should take into account the glycemic profile, with additional measures taken to prevent thrombosis (such as the use of an intermittent pneumatic compression device within a below-knee cast, early preoperative mobilization and administration of anticoagulants) and additional attention paid to the surgical wound. Standardization of procedures brings oncological benefits, but the personalization of surgery may be key to improving the rate of postoperative complications.

The limitation of the present study was the small number of cases examined after meeting the inclusion and exclusion criteria.

Table III. Histopathological findings.

| Variable | CRC cases (n=31) | | OR (95%CI) | P-value |
| | T2DM; n=30 (%) | No T2DM; n=31 (%) | | |
| --- | --- | --- | --- | --- |
| Tumor site | | | | |
| Right-sided | 7 (23.3) | 8 (25.8) | (Reference) | - |
| Left-sided | 14 (46.7) | 9 (29) | (Reference) | - |
| Rectum | 9 (30) | 14 (45.2) | | 0.222 |
| T | | | | |
| T1-2 | 9 (30) | 11 (35.5) | (Reference) | - |
| T2-3 | 21 (70) | 20 (64.5) | 0.779 (0.267-2.278) | 0.648 |
| N | | | | |
| N0 | 16 (53.3) | 12 (38.7) | (Reference) | - |
| N+ | 16 (46.7) | 19 (61.3) | 1.810 (0.654-5.009) | 0.252 |
| M | | | | |
| M0 | 27 (90) | 29 (93.5) | (Reference) | - |
| M+ | 3 (10) | 2 (6.5) | 0.621 (0.096-4.005) | 0.614 |
| Tumor stage | | | | |
| 1-2 | 15 (50) | 12 (38.7) | (Reference) | - |
| 3-4 | 15 (50) | 19 (61.3) | 1.583 (0.579-4.378) | 0.375 |

CI, confidence interval; CRC, colorectal cancer; M, pathological metastasis; N, pathological node; OR, odds ratio; T, pathological tumor; T2DM, type II diabetes mellitus.

Table IV. Univariate and multivariate analysis for patients with T2DM and CRC depending on the type of surgical approach.

| Variable | | Univariate analysis | | Multivariate analysis | |
| | Laparoscopy; n=8 (%) | Open; n=22 (%) | P-value | OR (95%CI) | P-value |
| --- | --- | --- | --- | --- | --- |
| ACCI | | | | | |
| <6 | 1 (12.5) | 2 (9.1) | | | |
| ≥6 | 7 (87.5) | 20 (90.9) | 0.787 | 1.429 (0.112-18.298) | 0.784 |
| Clavien-Dindo classification | | | | | |
| < Grade 3 | 8 (100) | 19 (86.4) | | | |
| ≥ Grade 3 | 0 | 3 (13.6) | 0.159 | 1.158 (0.981-1.367) | 0.040 |
| Surgical site infection | | | | | |
| Absent | 8 (100) | 19 (86.4) | | | |
| Present | 0 (18.4) | 3 (13.6) | 0.159 | 1.158 (0.981-1.367) | 0.040 |
| Anastomotic leakage | | | | | |
| Absent | 8 | 21 (95.5) | | | |
| Present | 0 | 1 (4.5) | 0.211 | 0.421 (0.290-0.611) | 0.271 |
| Pulmonary complications | | | | | |
| Absent | 8 (100) | 20 (90.9) | | | |
| Present | 0 | 2 (9.1) | 0.224 | 0.447 (0.314-0.637) | 0.144 |
| Ileus | | | | | |
| Absent | 7 (87.5) | 16 (72.7) | | | |
| Present | 1 (12.5) | 6 (27.3) | 0.008 | 0.237 (0.134-0.419) | 0.250 |
| Operation time, min[a] | 218.75±18.07 | 182.05±10.54 | 0.002 | | |
| No of lymph nodes retrieved[a] | 18.63±8.94 | 16±6.34 | 0.258 | | |
| Postoperative hospital stay[a] | 6.63±0.91 | 7.64±2.46 | 0.273 | | |

[a]Mean ± standard deviation. ACCI, age-adjusted Charlson comorbidity index; CI, confidence interval; CRC, colorectal cancer; OR, odds ratio; T2DM, type II diabetes mellitus.

Patients with a personal history of cancer, those with a family history of CRC and patients who presented to the Emergency Department with complications of colorectal tumors (stenosis, perforation or hemorrhage) and without histopathological diagnosis of malignancy, were not included in the present study because the surgical management of these patients is different from elective cases (predominant use of open surgery, performing colostomy/ileostomy or biological imbalances); the postoperative effect of possible complications cannot be analyzed with cases of elective patients, this making the contribution of another study. It would be premature to implement changes in the preoperative management of patients with DM based on these data alone. Further studies are needed to validate these findings.

In conclusion, diabetes predisposes patients to a higher incidence of postoperative complications, including surgical site infections and anastomotic leaks, with an increased length of hospital stay following CRC surgery. To improve postoperative results, laparoscopic surgery is recommended for patients with diabetes. In the future, developing a risk profile for diabetes prior to surgery and a perioperative management plan encompassing individualized measures should be considered.

## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Authors' contributions

RCP, NL, FB, ED, AD and AFM contributed to the conception and design of this study. RCP, NL, FB, CT, CB and AD were responsible for the data collection and analysis. RCP, NL, FB, ED and AFM oversaw drafting of the manuscript. RCP, NL, FB, AFM, CT, AD and CB revised the manuscript critically for important intellectual content. RCP and NL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The present study was approved by the Local Ethics Commission for the Approval of Clinical and Research Developmental Studies, County Clinical Emergency Hospital of Constanța, in accordance with the Declaration of Helsinki on experimentation with human subjects. Informed consent was obtained from all patients at the time of enrolment (approval no. 12/2020).

## Patient consent for publication

Informed consent was obtained from all patients at the time of enrolment.

## Competing interests

The authors declare that they have no competing interests.

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