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Pre- and postoperative characteristics of metabolic syndrome in patients with colorectal cancer

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Abstract: The pathological mechanisms that link the metabolic syndrome (MS) and colorectal cancer (CRC) are most probably related to abdominal obesity and insulin resistance. This study aimed to assess the relationship between MS and its clinical characteristics, with CRC. We investigated the changes in the appearance of MS features three months after surgical treatment, and its relationship with the concentration of tumor and inflammation markers. The retrospective cohort study was performed on 193 patients who were diagnosed with CRC and consequently surgically treated (at the Department of General Surgery, Clinical Hospital Center "Bežanijska kosa", Belgrade). The included patients were divided into two groups based on the presence of MS. Body mass index (BMI), waist circumference, blood pressure, blood glucose, triglycerides (TG), high density lipoproteins – cholesterol (HDL-C), carcinoembryonic antigen (CEA), α-fetoprotein (AFP), carbohydrate antigen 19-9 (CA 19-90) and C-reactive protein (CRP) were analyzed at the time when the CRC diagnosis was made and three months after surgery. We observed a significant decrease in the number of patients with MS three months postoperatively compared to the number of patients in the preoperative period (106 versus 81; $p<0.001$). CRP levels were significantly decreased postoperatively compared to the preoperative period in patients with MS ($p<0.001$). AFP concentrations were significantly decreased ($p<0.001$), while CEA and CA 19-9 were significantly increased postoperatively compared to preoperatively ($p<0.001$, $p<0.001$). Further studies should be conducted in order to examine the influence of MS and its characteristics solely on CRC prognosis and its overall effect on CRC treatment.

Key words: metabolic syndrome; colorectal neoplasms; preoperative period; postoperative period; biomarkers

INTRODUCTION

Metabolic syndrome (MS) represents a cluster of several metabolic diseases with insulin resistance as a mutual underlying pathophysiological process. The incidence of MS in the general population is about 17-25%, whilst in the United States it goes up to 35% [1]. In Serbia, the frequency of MS, with regard to overweight and advanced age, goes up to 60% in some parts of the country [2]. It is recognized as a predisposing factor for the development of many other diseases, predominantly for diabetes mellitus type 2 and cardiovascular diseases [3,4]. Previous studies described a potential association between MS presence and the risk for different cancer types evolving [5,6]. Furthermore, MS has been described as a potential risk factor for colorectal cancer (CRC) development [7]. The pathological mechanisms that link these two conditions are most probably related to abdominal obesity and insulin resistance [9,10].

CRC is one of the most frequent types of tumor worldwide [11]. In Serbia, CRC is the second most common cause of death, after lung cancer, in men, and the third most common cause of death, after breast and

cervical cancer, in women. The standardized mortality rate for CRC is estimated as 16.6/100000 in the Serbian population, and is almost 2-fold higher in men [12]. Surgical treatment is the method of choice for curing CRC patients. In many countries worldwide CRC screening was initiated in 1976, with an improving rate for detection over time [13]. To date, several tumor biomarkers have been used in the diagnosis of CRC [14]. Carcinoembryonic antigen (CEA), carbohydrate or cancer antigen 19-9 (CA 19-9) and α-fetoprotein (AFP) are one the most frequently exploited [15]. However, they have shown different levels of sensitivity and specificity depending on the stage of the CRC [16], use of chemotherapy [17], patients' habits [18] and the presence of nonmalignant diseases [19].

Numerous previous studies have investigated MS as a risk factor for CRC development, but only a few of them have evaluated possible changes in MS presence in CRC patients after tumor excision [9,10]. This study aimed to assess the relationship between MS and its clinical characteristic with CRC. Furthermore, we investigated changes in the appearance of MS features three months after the surgical treatment and its relationship with the concentration of tumor and inflammation markers.

MATERIALS AND METHODS

Patient selection and data sampling

The retrospective cohort study was performed on 193 patients who were diagnosed with CRC and consequently treated surgically. The analyzed period was from September 2013 to March 2016. All necessary medical data were collected from the patients' medical records at the Department of General Surgery, Clinical Hospital Center "Bežanijska kosa", Belgrade. The patients' sociodemographic data, including age at diagnosis, sex, alcohol and tobacco use and medical history for tumors, obesity and cardiovascular diseases, were observed. The tumor differentiation grade, Dukes' and Astler-Coller classification were employed for the staging of CRC. The study was approved by the Ethical Committee of the Faculty of Medicine, University of Belgrade.

The included patients were divided into two groups based on the presence of MS. MS was defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (20). It was diagnosed when three or more of the following criteria were met: (i) BMI > 25 kg/m2 with measurement of abdominal obesity: waist circumference >90 cm in men and >80 cm in women; (ii) triglycerides (TG) ≥150 mg/dL (≥1.7 mmol/L), or on drug treatment to decrease TG; (iii) high-density lipoprotein cholesterol (HDL-C) <40 mg/dL (<1 mmol/L) in men or <50 mg/dL (<1.3 mmol/L) in women or during drug treatment to reduce HDL-C; (iv) blood pressure ≥130/85 mmHg, or during drug treatment for hypertension; and (v) fasting blood sugar ≥110 mg/dL (≥6.1 mmol/L), or during drug treatment to decrease blood glucose. The values of tumor markers CEA, CA 19-9 and AFP, and inflammation marker, CRP, were observed in the two study groups. The cut-off value for CEA was 4.7 ng/mL, for AFP 5.8 IU/mL, for CA 19-9 39 U/mL and for CRP 10 mg/L. All investigated parameters were analyzed at the time when the CRC diagnosis was made and three months after surgical procedures.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows Software (Version 20.0< IBM Corp, Armonk, NY, USA). The χ^2 analysis was conducted to assess statistical significance between categorical data. The Wilcoxon signed-rank or Student t-test were used to determine statistical significance between numerical data. All p values less than 0.05 were considered significant.

RESULTS

Sociodemographic characteristics of patients

Sociodemographic characteristics for each group are summarized in Table 1. The study included 110 men (57%) and 83 women (43%), with an average age of 67.7±10.7 years. The group with metabolic syndrome consisted of 106 (54.99%) patients, while 87 (45.01%) patients did not meet the criteria for MS. The frequency of MS was significantly greater in women than in men with CRC (53.8% versus 46.2%; p<0.001). A positive family history for obesity was significantly increased in the group of patients with MS compared to

the group without MS (88.7% versus 11.3%; p<0.001). The mean age at diagnosis, alcohol intake and smoking, medical history for tumors and cardiovascular diseases did not show statistically significant differences between the groups with and without MS (Table 1).

The relationship between the degree of tumor differentiation, Dukes' and Astler-Coller staging and the presence of MS are given in Table 2. The majority of CRC patients with (58.5%) and without (60.9%) MS had a G2 degree of tumor differentiation. The observed difference was not statistically significant (p=0.762). We observed that the half of the CRC patients with MS had a C stage of Dukes' classification. On the other hand, an equal number of patients without MS were in Dukes' stages B (46.0%) and C (46.0%). Additionally, the observed differences were not statistically significant (p=0.565). Astler-Coller classification revealed that more than half of CRC patients with MS were at stage C (50.9%). On the other hand, the majority of CRC patients without MS (48.0%) were at stage B of the Astler-Coller classification. The observed difference was not statistically significant (p=0.842) (Table 2).

The characteristics of MS in CRC patients before and after surgery

The characteristics of MS among the patients with CRC in the analyzed periods are given in Table 3. We observed a significant decrease in the number of patients with MS after three months postoperatively as compared to the number of patients in the preoperative period (106 versus 81; p<0.001). The values of the anthropometric measures (BMI and waist circumference) were significantly decreased after treatment compared to the preoperative period in patients with MS (p<0.001, p<0.001, respectively). The levels of blood glucose and triglycerides were significantly decreased, while the levels of HDL-C were significantly increased at the postoperative evaluation compared to the pretreatment status (p<0.001, p<0.001, p<0.001, respectively). Additionally, the values of systolic blood pressure were significantly decreased three months after surgery compared to the values before treatment (p=0.004). Statistical analysis did not show a significant difference in the change of diastolic blood pressure values among the analyzed periods in patients with MS (Table 3).

Table 1. Sociodemographic characteristics of patients diagnosed with CRC.

Parameters		Metabolic syndrome (MS)		*p* value
		Yes (n=106)	No (n=87)	
Age at diagnosis (Mean±SD)		68.21±10.30	67.07±11.08	0.461[a]
Sex	Female	57 (68.7%)	26 (31.3%)	<0.001[b]
	Male	49 (45.5%)	61 (55.5%)	
Alcohol intake	yes	19 (17.9%)	87 (82.1%)	0.737[b]
	no	14 (16.1%)	73 (83.9%)	
Smoking	yes	92 (86.8%)	18 (20.7%)	0.164[b]
	no	14 (13.2%)	69 (79.3%)	
Family history for obesity	yes	94 (88.7%)	29 (33.3%)	<0.001[b]
	no	12 (11.3%)	58 (66.7%)	
Family history for tumor	yes	9 (8.5%)	5 (5.7%)	0.465[b]
	no	97 (91.5%)	82 (94.3%)	
Family history for MI	yes	7 (6.6%)	4 (4.6%)	0.757[b]
	no	99 (93.4%)	83 (95.4%)	
Family history for CVI	yes	3 (2.8%)	4 (4.6%)	0.703[b]
	no	103 (97.2%)	83 (95.4%)	

[a]Student t-test; [b]Chi-square test; Mn – mean, SD – standard deviation, n – number of cases, MI – myocardial infarction, CVI – cerebrovascular insult

Table 2. The relationship between the degree of tumor differentiation, Dukes' and Astler-Coller scales and the presence of MS.

		Metabolic syndrome (MS)		*p* value
		Yes n (%)	No n (%)	
Degree of tumor differentiation	G1	35 (33.0%)	29 (33.3%)	0.762[a]
	G2	62 (58.5%)	53 (60.9%)	
	G3	9 (8.5%)	5 (5.7%)	
Dukes' classification of tumor	A	2 (1.9%)	5 (5.7%)	0.565[a]
	B	48 (45.3%)	40 (46.0%)	
	C	53 (50.0%)	40 (46.0%)	
	D	3 (2.8%)	2 (2.3%)	
Astler-Coller classification of tumor	A	2 (1.9%)	3 (3.4%)	0.842[a]
	B	47 (44.3%)	42 (48.3%)	
	C	54 (50.9%)	40 (46.0%)	
	D	3 (2.8%)	2 (2.3%)	

[a]Chi-square test; G1 – well differentiated, G2 – moderately differentiated, G3 – poorly differentiated, Dukes' A – invasion into but not through the bowel wall, Dukes' B – invasion through the bowel wall penetrating the muscle layer but not involving lymph nodes, Dukes' C – involvement of lymph nodes, Dukes' D – widespread metastases, Astler-Coller A – limited to mucosa, Astler-Coller B – extending or penetrating into through the muscularis propria, Astler-Coller C – same as B with local metastases, Astler-Coller D – distant metastasis.

Levels of inflammatory and tumor markers in CRC patients before and after surgery

The changes in tumor and inflammation marker levels in CRC patients with and without MS in the analyzed periods are presented in Table 4. The values

Table 3. Characteristics of the MS in patients with colorectal cancer in pre- and postoperative periods.

Parameters	Metabolic syndrome (MS)		*p* value
	Preoperative period (n=106) (Mn±SD)	Postoperative period (n=81) (Mn±SD)	
BMI (kg/m^2)	25.68±3.64	24.74±2.95	<0.001[a]
Waist circumference (cm)	89.70±13.47	87.88±12.48	<0.001[a]
Triglycerides (mmol/L)	1.43±0.35	1.39±0.67	<0.001[b]
HDL (mmol/L)	1.44±0.33	1.8±0.32	<0,001[a]
Systolic BP (mmHg)	134.96±19.40	133.87±19.13	0.004[a]
Diastolic BP (mmHg)	81.22±10.53	81.40±9.99	0.401[a]
Blood glucose (mmol/L)	6.86±2.86	5.48±1.46	<0.001[a]

[a]Student t-test; [b]Wilcoxon signed rank test; Mn – mean, SD – standard deviation, n – number of cases, BMI – body mass index, HDL – high density lipoproteins, BP – blood pressure

of CRP were not significantly different between the CRC patients with MS compared to patients without MS in the preoperative period (15.73±32.70 versus 8.21±16.38; p=0.204). On the other hand, three months after surgery, the CRP level was significantly decreased in patients without MS compared to patients with MS (p<0.013).

The values of AFP and CEA were not significantly different among the CRC patients with regard to MS presence at the time of diagnosis and three months postoperatively (Table 4). Although the CA 19-9 concentrations were below the cut-off value in both groups (<39 U/mL), they were significantly higher in CRC patients with MS compared to patients without MS in both analyzed periods (21.37±13.54 vs. 17.03±10.15, 29.82±19.36 vs. 25.22±23.35; p=0.046, p=0.005, respectively).

The trend of tumor and inflammation marker levels in CRC patients with MS pre- and postoperatively are shown in Table 5. The CRP level was significantly lower three months after surgery compared to the preoperative level (p<0.001). Similarly, the AFP value was significantly lower postoperatively (p<0.001). On the other hand, values of CEA and CA 19-9 were significantly higher three months after treatment (p<0.001, p<0.001, respectively).

DISCUSSION

MS represents one of the major health problems worldwide with a growing incidence over time. This is mainly due to negative changes in life habits, such as an unbalanced diet and a lack of physical activity [21-23]. Additionally, these factors are recognized to be responsible for CRC development [24]. A previous study showed that regular physical exercise leads to a decrease in the presence of CRC [25].

The results of this study did not show a correlation between positive family history for myocardial infarction (MI), cerebrovascular insult (CVI) or tumors with the presence of CRC. Only obesity was significantly more prevalent among CRC patients' families, regardless of their MS status. In the twenty-first century, obesity is a disease of pandemic proportions that predominantly affects the developed world, but with increasing occurrence in third world countries [26]. Abdominal obesity is recognized as an independent

Table 4. Pre- and postoperative levels of tumor and inflammation markers in colorectal cancer patients with and without MS.

Parameters	Metabolic syndrome (MS)	Analyzed periods			
		Before surgery (Mn±SD)	P value	3 months postoperative (Mn±SD)	P value
CEA (ng/mL)	Yes	4.68±3.70	p=0.581[a]	5.00±5.80	p=0.435[a]
	No	4.31±1.81		4.66±5.68	
AFP (IU/mL)	Yes	10.29±9.74	p=0.294[a]	5.95±7.46	p=0.377[a]
	No	9.08±8.31		5.71±9.26	
CA 19-9 (U/mL)	Yes	21.37±13.54	p=0.046[a]	29.82±19.36	p=0.005[a]
	No	17.03±10.51		25.22±23.35	
CRP (mg/L)	Yes	15.73±32.70	p=0.204[a]	14.91±31.31	p=0.013[a]
	No	8.21±16.38		5.82±11.93	

[a]Mann-Whitney U test; Mn – mean, SD – standard deviation, n – number of cases, AFP – α-fetoprotein, CA 19-9 – cancer antigen 19-9, CEA – carcinoembryonic antigen, CRP – C-reactive protein

Table 5. Changes in tumor and inflammation marker levels in colorectal cancer patients with MS before and after treatment.

Parameters	Metabolic syndrome (MS)		*P* value
	Before surgery (n=106) (Mn±SD)	3 months postoperative (n=81) (Mn±SD)	
CEA (ng/mL)	4.52±3.00	4.84±5.73	<0,001[a]
AFP (IU/mL)	9.74±9.12	5.77±8.49	<0,001[a]
CA 19-9 (U/mL)	19.41±12.29	27.43±22.14	<0,001[a]
CRP (mg/L)	15.36±32.00	6.79±13.93	<0.001[a]

[a]Wilcoxon signed rank test; Mn – mean, SD – standard deviation, n – number of cases, AFP – α-fetoprotein, CA 19-9 – cancer antigen 19-9, CEA – carcinoembryonic antigen, CRP – C-reactive protein

risk factor for atherogenic and metabolic abnormalities in youth [27]. Furthermore, recent studies found an association between excessive fatness and the risk for MS and CRC [28].

At the time of CRC diagnosis, slightly more than half of our patients were also diagnosed with MS. Although there were more men with CRC, a significantly larger number of women met the criteria for MS. Three months after surgical treatment we found the percentage of patients with three or more MS characteristics significantly decreased. Two earlier studies showed an increased risk of CRC mortality with an increase in MS features compared to their sole influence, suggesting their possible additive or synergistic effect [7,8]. Additionally, this study analyzed the potential effect of MS on the degree of tumor differentiation and level of tumor stage at the time of CRC diagnosis. Our results showed no significant correlation between these investigated tumor parameters and the presence of MS. Such findings suggest that MS does not contribute to CRC invasiveness and the degree of differentiation.

Our results showed that the concentration of TG, HDL-C and blood pressure values were significantly different pre- and postoperatively. All of them showed significant amelioration after surgical treatment. Two earlier studies showed the correlation between unregulated blood pressure and CRC [7,29]. Grossman et al. [30] reported that hypertension increased the risk of overall cancer mortality by 23%. Several studies showed a significant link between TG level and adenoma development, predominantly in Asian population [31-33]. In addition, Bayerdorffer et al. [34] found a 2- to 3-fold increased risk for CRC development in patients with low HDL-C concentration. Pooled results of a meta-analysis [9] have shown that high concentrations of TG and low HDL-C, independently present a lower risk for CRC in comparison with MS.

Other characteristics of the MS (increased blood glucose concentration, BMI and waist circumference) in our study were significantly increased before treatment. Esposito et al. [9] showed that individuals with hyperglycemia and/or a pathological waist circumference should be more closely observed during CRC screening. Also, our results are in accordance with previous studies showing the possible role of increased glucose levels and insulin resistance in CRC pathogenesis [9,35]. Trevisan et al. [8] reported that, besides other components of MS, only increased glucose concentrations were associated with an increased risk of death in CRC patients. Other studies showed that elevated fasting insulin levels in patients without diabetes mellitus are significantly and independently associated with the development of a different type of cancers, including CRC [36-39]. There are several mechanisms whereby insulin resistance may be responsible for CRC development: the ability of insulin to translocate the Ras protein on the cell membrane, the susceptibility of tumor cells to the growth effects of insulin in cooperation with insulin-like growth factor 1 (IGF-1) inhibition of the synthesis of sex hormone-binding globulin (SHBG), which leads to increased bioavailability of androgens and estrogens, hormones that play a role in the pathogenesis of CRC [39,40]. Cancer cells have high demands for glucose and are recognized as cells with an accelerated metabolic state. Hyperglycemia leads to an environment of excess energy in the body, which promotes the proliferation of tumor cells [5]. Furthermore, elevated glucose levels promote the formation of reactive oxygen species (ROS), which can damage DNA and thus lead to cancer development [41]. Additionally, it is suggested that hypertriglyceridemia may have an influence on excessive ROS production and thereby have its part in promoting carcinogenesis [42].

Calle et al. [40] described increased BMI (>25 kg/m^2) as being responsible for higher mortality rates in many types of cancers, including CRC. BMI as a clinical feature has two imperfections: an inability to distinguish between fat and lean body mass, and ignoring body fat distribution [43]. On the other hand, waist circumference is a direct reflection of the amount of

abdominal obesity (a reflection of visceral fat distribution). The European Prospective Investigation into Cancer and Nutrition (EPIC) has proposed that abdominal obesity (measured as waist circumference or the waist-to-hip ratio) is an equally strong risk factor for colon cancer for both sexes [44].

Previous studies have shown abdominal or central obesity to be responsible for higher risk in colorectal adenoma development [45,46]. Visceral adipose tissue, which is physiologically more active than peripheral subcutaneous fat, is recognized as an endocrine tissue, leading to hormone and cytokine production with inflammatory and metabolic potential [47]. Proinflammatory cytokines, tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and adiponectin, which are produced in visceral adipose tissue, promote the development of chronic subclinical inflammation [48]. In obese individuals, it provides an environment which favors the development of MS by inflammation [49]. TNF-α and IL-6 induce the liver to produce an acute-phase protein, the C-reactive protein (CRP) [50]. A link between colonic areas with chronic subclinical inflammation and sporadic colorectal neoplasia has been suggested. Itzkowitz et al. [51] reported the evidence for chronic inflammation as the main predisposing factor for CRC in inflammatory bowel disease (IBD). Our findings showed a 2.26-fold decrease in CRP three months postoperatively. These results, together with the reduction in the number of patients with MS and significantly decreased BMI (by 1 kg/m^2, respectively), are in agreement with previous studies indicating that weight loss leads to the suppression of inflammatory processes. In addition, our results suggest that the presence of CRC provokes the inflammatory response and consequently leads to an increment of CRP values. This is supported by the lower CRP levels and changes in colorectal mucosa [52,53].

Currently, there are a large number of tumor markers used for the early detection, diagnosis and prognosis of CRC, as well as prediction of the efficacy of different therapeutic protocols, survival rate and disease relapse. To date, none of the tumor biomarkers shows enough specificity and sensitivity for CRC screening [14]. CEA is one of the most used tumor markers in CRC screening. Its specificity for diagnosis is shown to be around 90% and sensitivity between 40% and 75% [15]. However, the use of CEA has some limitations. It could be produced by other malignant and benign epithelial tumors, as well as some inflammatory processes, such as IBDs, pancreatitis, lung infections and liver diseases [54]. Herrera et al. [55] showed that a high preoperative level of CEA is an indicator of advanced stage and low differentiation grade of a tumor.

CA 19-9 was first recognized in 1979 as an additional marker for CRC follow-up [56]. Previous investigations revealed the significantly lower specificity and sensitivity of CA 19-9 compared to CEA [57]. Unlike CEA, CA 19-9 is significantly lower in smokers [18]. Also, its values could be increased in patients with poorly controlled diabetes mellitus, regardless of tumor presence [19]. Unlike CEA and CA 19-9, the AFP biomarker is not commonly used in CRC screening. Normally, it is produced during the fetal period by the liver and yolk sac [58]. It is mostly used for the diagnosis of hepatocellular cancer, hepatoblastoma and yolk sac tumors [59].

Our results showed a significant decrease in AFP values three months after treatment in patients with MS. On the other hand, CEA and CA 19-9 concentrations were significantly higher after the treatment. This could be due to the rest of the tumor, undetectable metastasis or some other inflammatory process which took place at the time of blood sampling postoperatively. We did not include some of the radiological imaging techniques that could give a more comprehensive explanation of the patients' postoperatively status. According to our results, pre- and postoperatively, MS presence did not additionally influence AFP and CEA levels. On the other hand, even if its concentrations were below the cut-off value, CA 19-9 was significantly higher in the MS group in both analyzed periods. Such findings might suggest the possible influence of metabolic changes on CA 19-9 production. To date, there is no research regarding follow-up in tumor marker level changes pre- and postoperatively in CRC patients in the presence of MS. Future studies are needed to evaluate the correlation of tumor markers and MS within CRC screening programs.

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