

## Association of colorectal carcinoma and metabolic syndrome

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### ABSTRACT

**Aim** Colorectal carcinoma is one of the most common neoplasms, especially in Western countries and those with westernisation. On the other hand, high rate of metabolic syndrome (MetSy) has also been noticed, as well as in Western countries. It seems like these two conditions are somehow connected. In this study, we wish to explore some characteristics of colorectal carcinoma and its correlation with MetSy.

**Methods** In this retrospective study the data were taken from medical records of 67 patients with colorectal carcinoma, and for 30 healthy controls. Input parameters of patients were compared mutually, as well as with parameters of healthy, control examinees that had negative screening colonoscopy for neoplasm.

**Results** Average age of patients was 68 years. The most frequent localisation of neoplasm was on rectum (53.7%) and most frequent level was Dukes C (38.8%). The patients had MetSy more frequently when compared with controls ( $p=0.048$ ), and also they had more MetSy components ( $p=0.006$ ). The link between MetSy and localisation of neoplasm was not found, neither with its pathohystological characteristics.

**Conclusion** Patients with MetSy should be warned about the increased risk of colorectal carcinoma, and, in this way, motivated for earlier and more frequent screening colonoscopies, as well as of a change of unhealthy lifestyle.

**Key words:** colorectal surgery, colonoscopy, diabetes mellitus, hypertension, abdominal obesity

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## INTRODUCTION

Colorectal carcinoma is one of the most frequent neoplasms worldwide. According to many authors, it is the third most frequent carcinoma with increasing incidence (1,2). Recent researches have shown that incidence of colorectal carcinoma is increasing in countries with rising economic standard; on the other hand, it is stable or decreasing in the most developed countries (3). Occurrence of colorectal carcinoma has been linked, like many other malignant neoplasms, with genomic mutations which are targeting tumour suppressor genes and/or proto-oncogenesis of normal epithelial mucosa cells of colon (4). These mutations are cumulative, so after certain time, they lead to changes of colonic mucosa. Colorectal carcinoma starts as hyperplasia of colonic mucosa, as a polyp in which mutations occur continuously, leading to dysplasia or malignant alteration eventually (5). Some of those neoplasms are linked with inherited mutations, as it is known in cases of adenomatous polyposis, but most of them are caused by mutations over time in those individuals with more prominent risk factors. Risk factors for developing colorectal carcinoma are age, inflammatory bowel disease, sedentary lifestyle and absence of physical activity, obesity, and unhealthy food with lots of red meat, consumption of alcohol and tobacco products (6). More attention has been paid to the colonic microbiome, as well as to its deregulation, in the role of colorectal cancer development (7). Symptoms of colorectal cancer are various and depend on localisation and stage of the disease. Most of them are diagnosed when disease has advanced, which negatively reflects mortality and medical costs, therefore screening colonoscopies are recommended for general population of the age of 50 and above (8).

Metabolic syndrome (MetSy) is also a frequent condition, and it seems that both conditions share some common characteristics. MetSy is a cluster of components which occur because of overeating and sedentary lifestyle that, in the end, result in obesity. Components of MetSy are abdominal obesity, insulin resistance, dyslipidaemia, elevated blood pressure, prothrombin and pro-inflammatory state (9). In the modern era, MetSy has become the most important source of new diabetic patients, and also an important cause of cardiovascular diseases. Apart from diabetes type 2 and cardiovascular diseases, persons with

MetSy seem to be susceptible for developing some other conditions, such as polycystic ovarian syndrome, fatty liver, gallstones, asthma, sleep disorders and some types of carcinomas (10,11). MetSy is frequent worldwide, with prevalence of 10-40%, depending on different populations throughout the world (12). It is well known that MetSy takes epidemic proportions in countries which are marked to be characterized with overeating and absence of physical activity within their population. About 15% of population at the age 40-75 in those countries have MetSy (13).

The aim of this study was to determinate the association of colorectal carcinoma (its pathohistological characteristics) and MetSy (and its components) in the population of patients, and to compare results with control, healthy examinees without colorectal carcinoma.

## PATIENTS AND METHODS

### Patients and study design

There were 97 examinees in this retrospective study. An experimental group included 67 patients with verified colorectal carcinoma, who were diagnostically processed and underwent surgery at the University Hospital of Mostar in the period January 2017 to December 2018. A control group included 30 persons who underwent screening colonoscopy, with exclusion of the presence of colorectal neoplasm.

The patients were included in the study after a pathohistological diagnosis and Dukes classification.

The study was conducted in accordance with the Declaration of Helsinki and principles of good clinical practice, with a permission of the Ethical Committee of the Clinical Hospital of Mostar.

### Methods

Experimental group data were taken from Hospital's medical records, and for control group data were taken from the Primary Care Medical Centre records, registered by general practitioners. Both groups underwent colonoscopy at the University Clinical Hospital Mostar. Patients were hospitalized and colonoscopy was made as a preparation for operation. Controls were sent by general practitioner for screening colonoscopy. The following data were taken: age (under 30; 31-40; 41-50, 51-60, 61-70, and above 70), gen-

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der, height, weight, body mass index (BMI), and waist circumference, laboratory test results necessary for the diagnosis of MetSy and blood pressure values, information about previously diagnosed hypertension and diabetes mellitus. Also, for the patients group the data about colorectal carcinoma were taken: localisation of neoplasm, Dukes grade, differentiation of neoplasm.

According to NCEP-ATP III (National Cholesterol Education Program-Adult Treatment Panel III) the diagnosis of MetSy is based on the simultaneous occurrence of three or more of the following components (14): waist circumference  $\geq 102$  cm in men or 88 cm in women; serum triglycerides  $\geq 1.7$  mmol/L; serum high density lipoprotein (HDL) cholesterol  $< 1.04$  mmol/L in males or  $< 1.30$  mmol/L in females; blood pressure  $\geq 130/85$  mmHg; fasting glucose level  $\geq 6.1$  mmol/L.

Patients who have already used antihypertensives or oral hypoglycemics are considered to fulfil the criteria for hypertension and hyperglycemia.

### Statistical analysis

The data were processed by descriptive, parametric and non-parametric statistical methods, depending on the distribution of the results. The statistical tests used were Chi-square, Student T-test, and Odds ratio. The probability of  $p < 0.05$  was taken as statistically significant.

### RESULTS

The group of patients consisted of 42 men and 25 women ( $p = 0.038$ ), while the control group consisted of 12 men and 18 women ( $p = 0.273$ ).

Median age of the patients was  $68.1 \pm 10.91$  years, and controls  $54.31 \pm 16.85$  years of age ( $p < 0.00$ ). After grouping examinees by age groups, it was found the controls were equally distributed in every group ( $p = 0.669$ ), but the highest number of patients was in the group 70 years and above ( $p = 0.000$ ).

There was no statistical difference in average values of height, weight, BMI between patients and controls according to gender (Table 1).

Regarding localisation of colorectal carcinoma, the most frequent place of carcinoma was rectum, in 36 (53.7%) cases, followed by caecum and ascending colon in 14 (20.9%), sigmoid colon in nine (13.4%) cases, and the least frequent

**Table 1. Comparison of average values of height, weight and body mass index (BMI) of patients and controls according to gender**

Variable	Group	Mean ( $\pm$ SD)	p
<b>Male</b>			
Weight	Patients	82.90 (13.57)	0.949
	Controls	82.62 (12.32)	
Height	Patients	180.97 (6.61)	0.923
	Controls	180.75 (8.44)	
BMI	Patients	25.31 (4.24)	0.950
	Controls	25.22 (3.94)	
<b>Female</b>			
Weight	Patients	71.62 (13.59)	0.931
	Controls	72.00 (14.86)	
Height	Patients	165.95 (4.95)	0.462
	Controls	167.22 (6.08)	
BMI	Patients	25.54 (5.32)	0.957
	Controls	25.63 (4.43)	

localisation was on transversal and descending colon, in five (7.5%) and three (4.5%) cases, respectively ( $p = 0.528$ ) (Table 2).

**Table 2. Metabolic syndrome (MetSy) and neoplasm location**

Neoplasm location	No (%) patients		
	With MetSy	Without MetSy	Total
Caecum and ascending	9 (13.4)	5 (7.4)	14 (20.8)
Transversal	3 (4.4)	2 (2.9)	5 (7.4)
Descending	2 (2.9)	1 (1.4)	3 (4.4)
Sigmoid	4 (5.9)	5 (7.4)	9 (13.4)
Rectum	20 (29.8)	16 (23.8)	36 (53.7)
<b>Total</b>	<b>38 (56.7)</b>	<b>29 (43.2)</b>	<b>67 (100)</b>

Out of the total number of patients, 15 (22.4%) had colorectal carcinoma of Dukes A stage, nine (13.4%) Dukes B stage, 26 (38.8%) Dukes C stage, and 17 (25.4%) Dukes D stage ( $p = 0.091$ ) (Table 3).

**Table 3. Metabolic Syndrome (MetSy) and stage of colorectal carcinoma according to Dukes**

Dukes level	No (%) patients		
	With MetSy	Without MetSy	Total
A	6 (8.9)	9 (13.4)	15 (22.4)
B	5 (7.4)	4 (5.9)	9 (13.4)
C	15 (22.3)	11 (16.4)	26 (38.8)
D	12 (17.9)	5 (7.4)	17 (25.4)
<b>Total</b>	<b>38 (56.7)</b>	<b>29 (43.2)</b>	<b>67 (100)</b>

Out of the total number of patients, 15 (22.4%) had distant metastases of colorectal carcinoma, while 52 (7.6%) did not have any detected metastases. Neoplasm was differentiated well in 40 (59.7%), while in 27 (40.3%) cases it was poorly differentiated.

The presence of metabolic syndrome in relation to group affiliation was statistically significant ( $p = 0.048$ ) (Table 4). By calculating OR (odds ratio), examinees with MetSy were 2.62 times more likely to have colorectal carcinoma.

**Table 4. Presence of metabolic syndrome (MetSy) in the group of patients and controls**

MetSy	No (%) of patients		
	Patients	Controls	Total
Yes	38 ( 56.7)	10 (33.3)	48 ( 49.5)
No	29 (43.3)	20 (66.7)	49 ( 50.5)
<b>Total</b>	<b>67 ( 100)</b>	<b>30 ( 100)</b>	<b>97 ( 100)</b>

p=0.048

The components of MetSy were found more frequently in the patient group comparing to the control group: without components there were five patients and 11 controls, with one component, 12 patients and 7 controls, and with two components 12 patients and four controls. Three components were found in 28 patients and five controls, four components in six patients and one control, and all five components in four patients and two controls (p<0.00).

Waist circumference (considered as the first component) above the set criteria was found in 41 patients compared to 11 controls, and 26 patients and 19 controls had normal waist circumference (p=0.03). The second MetSy component that was considered was HDL value, and it was found that 30 patients had it less than the set criteria compared to 13 controls, and 27 patients 17 healthy subjects had normal HDL values (p=0.586). Considering the values of triglycerides, 36 patients and 15 controls were above desirable values, while 44 patients and 15 controls had normal values (p=0.04).

**Table 5. Comparison of average values of indicators for metabolic syndrome (MetSy) between the patients and controls**

Variable	Group	Mean ( $\pm$ SD)	p
Waist circumference	patients	100.56 (14.32)	0.00
	controls	88.00 (14.86)	
Systolic blood pressure	patients	136.75 (18.40)	0.04
	controls	125.67 (11.94)	
Diastolic blood pressure	patients	80.83 (10.29)	0.02
	controls	75.50 (9.68)	
Blood glucose	patients	6.85 (2.37)	0.003
	controls	5.43 (1.18)	
High density lipoprotein cholesterol	patients	1.12 (0.29)	0.039
	controls	1.34 (0.45)	
Triglycerides	patients	1.50 (0.59)	0.05
	controls	1.79 (1.02)	

Regarding comorbidities which accompanied both colorectal carcinoma and MetSy, the patients were significantly more likely to have arterial hypertension, in 43 (64.2%) cases within the group, unlike the controls, with 10 (33.3%) cases (p=0.002). The presence of hypertension as a comorbidity increases the risk of colorectal carcinoma by 4.09 times. In case of diabetes mellitus, it was also found that the patients had it significantly more often com-

paring to the controls, 24 (35.8%) and 5 (16.7%), respectively; diabetes mellitus increased the risk of colorectal carcinoma by three times (p=0.043). After comparison of average values of indicators for MetSy between patients and controls, most of them were statistically significant (Table 5).

## DISCUSSION

In this study, predomination of men in the patients with colorectal carcinoma was noticed like in other larger studies (15,16). Presumption is that men are more exposed to risk factors for developing colorectal carcinoma, and their hormonal state also contributes in some way to it (15,16).

Old age is a risk factor for itself, and in this study we obtained results which are compatible with other studies (17,18). Average age of patients, which was 68 years, was almost the same as in two larger studies from the UK (17,18). Due to that fact, we can expect an increasing incidence of colorectal carcinoma accompanying the increasing age (19). The average age of our control subjects was statistically significantly lower than the study group. The reason might be that our control subjects went for the screening, and it is our practice to do it before the age of 50 (20).

In this study we found that the most frequent location of colorectal carcinoma was rectum, Dukes C stage, well differentiated neoplasm without distant metastases at the current examination. Similar results were found in patients with colorectal carcinoma from Oman (21), where rectal carcinoma was also the leading location, as well as stage three, which is compatible with Dukes C; authors classified differentiation of colorectal carcinoma in three stages, while we classified it in accordance with new algorithms in two stages. Nevertheless, those two studies are comparable and also suggest that less than a half of tested neoplasms have poor differentiation. The examinees of Oman study, very similar to ours, were without distant metastases in 63.77% cases of carcinoma of colon, and 77% cases of rectal carcinoma (21).

The connection between overweight and incidence of carcinoma, especially of gastrointestinal system, has already been proven. The link between those two conditions is, besides the intake of carcinogens through overeating, disturbance of intestinal flora and chronic inflammation supported by fat tissue as pro-inflammatory organ (22,23). In this study,

there were no differences between patients and controls considering weight and BMI, but it can be noticed that average values within both groups were higher than normal. However, an important difference was noticed in results of waist circumference measurements, which were significantly higher in the patients' group. In a large Norwegian study, patients with colorectal carcinoma had BMI  $27.0 \pm 4.1$  and waist circumference  $90.7 \pm 11.8$ , that was very similar to our results; authors also considered other anthropometric parameters, and concluded that abdominal obesity was linked to and increased risk of colorectal carcinoma, especially in men. On the other hand, muscularity seems to have negative relation with colorectal carcinoma (24). Overweight represents introduction to MetSy, primarily in those individuals who have central accumulation of body fat (25).

The association between colorectal carcinoma and impaired serum lipid levels in this study is unclear. Our results imply that half of both patients and controls have impaired values, but without statistical significance, so we cannot make a clear conclusion. Reduced HDL and elevated triglyceride levels would be expected to be found in a patient group, but many factors are likely to affect their lipid status: catabolism due to malignancy, abrupt change in eating habits after cognition about malignant illness, starvation before preparations for colonoscopy. But neither larger studies nor ours are consistent on this point (26). There is a somewhat more convincing association between disturbed serum lipids and colorectal adenomas, which are firmly believed to be precursors of colorectal carcinomas (27).

Many studies, including ours, confirm that patients with colorectal carcinoma have MetSy more frequently, but they also have more of its components (28). Risk of developing colorectal carcinoma in patients with MetSy is about 1.5 times higher for both genders (28,29), but in our study it was as high as 2.62 times. Also, colonoscopy of elderly people with MetSy showed high prevalence of adenomatous polyps and colorectal carcinomas, compared to those without MetSy (30). Numerous molecular mechanisms which increase the risk of colorectal carcinoma are stated for the patients with MetSy. Among them, pathophysiological mechanism of oxidative stress, insulin-like growth factor, and inflammatory cytokines were

particularly noted (29). Visceral fat tissue acts in pro-oncogenic manner, probably because of leptin secretion, and is also connected with more aggressive types of tumours, especially in men (31).

Prevalence of hypertension in patients with colorectal carcinoma is different worldwide (32), and our results are respectively high. The conclusion is the same for diabetes mellitus. A study conducted in Iran on 1 127 000 patients with colorectal carcinoma reports that 13.38% had diabetes mellitus type 2, and 8.69% had hypertension. A study from Malaysia on 138 cases reports about 34.8% persons suffering from hypertension among the patients with colorectal carcinoma (32,33). In multicentre British study, prevalence of hypertension in the group of patients with colorectal carcinoma was 43% (18). Hypertension in patients with colorectal carcinoma was connected with mutual risk factors, as well as with some insufficiently clarified factor in pathogenesis of this disease (34,35). Changing food intake habits and introducing certain medication that lower blood pressure also reduce incidence of colorectal carcinoma (34). Elevated values of blood pressure, according to a study carried out by Lin et al. can be considered as an independent predicting factor for recurrent adenomatous polyps of colon, which are proven precancerous lesions of colorectal carcinoma (36). By exploring influence of blood pressure value on survival of patients with rectal carcinoma it was found that patients with lower values also have a higher chance of survival (37).

Diabetes mellitus type 2 is a very common comorbidity in patients with colorectal carcinoma (32). Although the connection between diabetes mellitus type 2 and colorectal carcinoma is still unclear, at least two pathways have influence on the development of colorectal carcinoma in patients with diabetes mellitus. The first pathway is reactive hyperinsulinemia which increases circulating IGF-1- proven stimulator of colonic epithelial cells. The second mechanism is hyperglycaemia, which is conducive to malignant cells whose metabolism is increased and dependent on high glucose intake (38). Anyway, overeating and unhealthy food, and consequent obesity are an introduction to diabetes mellitus, hypertension, MetSy. All those conditions intensify one another and are conducive to the development of colorectal carcinoma (39).

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In conclusion, a strong connection between MetSy and colorectal carcinoma was confirmed once more. Due to this fact, it would be good for individuals with MetSy to be sent to screening colonoscopies more frequently and most certainly before 50 years of age. It is also instructive to inform the patients with MetSy about an increased risk of developing colorectal carcinoma, and to try motiva-

ting patients to start a healthier lifestyle, physical exercise and appropriate food intake.

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## TRANSPARENCY DECLARATION

Competing interests: None to declare.

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