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ORIGINAL ARTICLE

A study on relationship between metabolic syndrome and colorectal cancer

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Summary

Purpose: *To investigate the effects of metabolic syndrome (MS) and its components on the pathological manifestations and metastasis of colorectal cancer (CRC).*

Methods: *Clinical and pathological data of inpatients with CRC admitted to our hospital from January 1st 2010 to December 31st 2017 were collected, including the patients' general information, initial symptoms, previous history, family history, whether MS or related components were complicated, endoscopic description, imaging diagnosis, pathological diagnosis and metastasis. According to the diagnostic criteria of MS, the patients were divided into MS group and non-MS group, and then patients in non-MS group were further grouped based on whether they met MS single component. The clinical and pathological characteristics in each group were analyzed by SPSS 20.0 statistical software.*

Results: *Among 1528 CRC patients, 76 (4.9%) were complicated with MS. CRC patients complicated with MS and those complicated with hypertension alone or diabetes alone were diagnosed at higher age, and most of them were elderly ($p<0.05$). CRC patients with body mass index (BMI) ≥25 kg/m² were diagnosed at lower age ($p<0.05$). The infiltration depth of CRC patients with diabetes was higher than that in the non-diabetic group, and it was more likely to invade the whole layer ($p<0.05$). The locations of CRC lesions in different BMI subgroups, fatty liver and nonfatty liver subgroups had statistically significant differences ($p<0.05$). In BMI ≥25 kg/m² group, CRC was mostly located in the left colon and rectum, while it was mostly located in the rectum in CRC patients with fatty liver.*

Conclusion: *Reducing the occurrence of MS and its components can reduce the incidence of CRC, and reduce its pathological manifestations and affect its metastasis at the same time.*

Key words: *oBMI, CRC, diabetes, fatty liver, hypertension, MS*

Introduction

Metabolic syndrome (MS) refers to a group of clinical syndromes in which diabetes or glucose tolerance, hypertension, dyslipidemia, and obesity are the main manifestations, insulin resistance (IR) is the common pathophysiological basis, and multiple metabolic diseases appear together [1-4]. In recent years, some authors have also proposed that nonalcoholic fatty liver disease (NAFLD), chronic inflammation, and prethrombotic state should also be included to metabolic syndrome [5,6]. At present, a large number of studies have shown that diabetes, obesity, etc., are associated with the incidence of colorectal cancer (CRC), but there are relatively few clinical studies on the effects of hypertension, dyslipidemia, and non-alcohol fatty liver disease (NAFLD) on the pathogenesis of CRC [7,8]. Therefore, this study intended to investigate and analyze the medical history data of CRC patients: 1) Patients with MS were classified as MS group and the rest were classified as non-MS group to observe whether there were significant differences in pathological manifestations and metastasis between the

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two groups. 2) In non-MS group, patients were divided into subgroups according to whether they had hypertension, diabetes, fatty liver and whether BMI was normal, and the pathological manifestations and metastasis were compared among groups to see whether there were significant differences.

Methods

Subjects

Clinical and pathological data of 1528 patients with CRC in Beijing Tiantan Hospital from January 1st 2010 to December 31st 2017 were collected and analyzed, including the patients' general information, initial symptoms, previous history, family history, whether MS or related components were complicated, endoscopic description, imaging diagnosis, pathological diagnosis and metastasis. All the patients included in this study were diagnosed with CRC by surgical pathology or imaging examination. Signed informed consent was obtained from all participants before the study. This study was approved by the ethics committee of Beijing Tiantan Hospital.

MS diagnostic criteria

Those who had 3 or all of the following 4 components could be diagnosed with MS: (1) Overweight or obesity: BMI ≥25 kg/m^2; (2) Hyperglycemia: fasting plasma glucose (FPG) ≥6.1 mmol/L and/or 2-h plasma glucose (PG) ≥ 7.8 mmol/L, and/or those who have been diagnosed with diabetes and treated; (3) Hypertension: systolic blood pressure/diastolic blood pressure (SBP/DBP) ≥140/90 mmHg, and/or those who have been diagnosed with hypertension and treated; (4) Dyslipidemia: fasting blood triglyceride (TG) ≥1.7mmol/L, and/or fasting blood high density lipoprotein-cholesterol (HDL-C) <0.9 mmol/L (males) or <1.0 mmol/L (females). All patients with fatty liver were diagnosed by upper abdominal computed tomography (CT) or B ultrasound.

Statistics

All statistics were performed using SPSS 20.0 software (IBM, Armonk, NY, USA). The t-test was performed for the comparison of continuous data and x^2 test for the count data. p<0.05 suggested that the difference was statistically significant.

Results

Comparison between MS group and non-MS group

Among a total of 1528 patients with CRC, 76 (4.97%) patients were complicated with MS. Among them, there were 93 (6.09%) patients with CRC family history, and there was no significant difference in CRC family history between MS group and non-MS group (p>0.05). There were more CRC patients aged over 60 years at the time of diagnosis in MS group than that in non-MS group (p=0.013, Table 1). There were no significant differences in histological grade, metastasis, infiltration depth and lesion location between the two groups (p>0.05, Table 1).

Comparison between hypertensive patients and non-hypertensive patients in the non-MS group

In the non-MS group, 467 (32.16%) CRC patients were complicated with hypertension, while 705 (67.84%) CRC patients had no hypertension. Among patients without MS, CRC patients with hypertension were older than those without hypertension at the time of diagnosis (p=0.001, Table 2). There were no significant differences in gender, histological grade, metastasis, infiltration depth and lesion location between the two groups (p>0.05, Table 2).

Comparison between diabetic patients and non-diabetic patients in the non-MS group

There were 137 (9.44%) CRC patients with diabetes and 1315 (90.56%) CRC patients without diabetes in the non-MS group. There was a statistically significant difference in infiltration depth between diabetic group and non-diabetic group (p=0.008, Table 3). The degree of infiltration was higher in patients with diabetes than that in those without diabetes. The age of CRC patients with diabetes at the time of diagnosis was higher than that of those without diabetes (p=0.000, Table 3). There were no statistically significant differences in gender, histological grade, metastasis, and lesion location between the two groups (p>0.05, Table 3).

Comparison between patients with BMI ≥25kg/m^2 and BMI <25kg/m^2 in the non-MS group

There were 327 CRC patients (22.52%) with BMI ≥25 kg/m^2 and 805 CRC patients (77.48%) with BMI <25 kg/m^2 in the non-MS group. CRC patients with BMI≥25 kg/m^2 were diagnosed at lower age than those with BMI<25 kg/m^2 (p=0.006, Table 4). The difference in lesion location between the two groups was statistically significant (p=0.002, Table 4), CRC was mostly located in the left colon and rectum in BMI ≥25kg/m^2 group. There were no significant differences in gender, histological grade and metastasis between the two groups (p>0.05, Table 4).

Comparison between fatty liver patients and non-fatty liver patients in the non-MS group

There were 97 (9.37%) cases of fatty liver and 942 (90.63%) cases of non-fatty liver in CRC patients in the non-MS group. There was a statistically significant difference in lesion location of patients without MS between fatty liver group and

Table 1. Comparison between MS group and non-MS group

	MS (n=76) *n (%)*	*Non-MS (n=1452)* *n (%)*	*p value*
Histological grade			0.224
I	0 (0)	38 (2.62)	
II	50 (65.79)	870 (59.92)	
III	26 (34.21)	522 (35.95)	
IV	0 (0)	22 (1.52)	
Metastasis			0.579
No metastasis	42 (55.26)	816 (56.20)	
Only lymph node metastasis	23 (30.27)	520 (35.81)	
Only single distant metastasis	5 (6.58)	35 (2.41)	
Multiple metastases	6 (7.89)	81 (5.58)	
Infiltration depth			0.485
Submucosa	6 (7.89)	141 (9.71)	
Intrinsic muscularis	13 (17.11)	237 (16.32)	
Slurry layer	27 (35.53)	495 (34.09)	
Whole layer and surrounding fibrous fatty tissue	30 (39.47)	579 (39.88)	
Lesion location			0.362
Right colon	19 (25.00)	340 (23.42)	
Left colon	26 (34.21)	348 (23.97)	
Rectum	29 (38.16)	740 (50.96)	
Multiple sites	2 (2.63)	24 (1.65)	

MS: metabolic syndrome

non-fatty liver group (p=0.015, Table 5). The lesions of CRC patients with fatty liver were located in the rectum. There were no significant differences in age, gender, histological grade, metastasis and infiltration depth between the two groups (p>0.05, Table 5).

Discussion

More and more research revealed that MS is closely related to colorectal neoplasms [7,9-11]. A retrospective analysis of CRC discovered that MS is an important independent risk factor for the prognosis of CRC [10]. A case-control study has shown that the risk of CRC in MS patients was increased by 1.64 times compared with that in patients without MS. Moreover, studies have also shown that the incidence of CRC in people with obesity, hypertension and hyperglycemia was 2.57-fold higher that in patients without such diseases [9,10].

At present, it is generally believed that the mechanism of correlation between MS and pathogenesis of CRC may be due to abnormalities of some endocrine hormones, such as insulin resistance (IR) and leptin [3,4,7]. Hyperinsulinemia induced by IR can increase the level of type-1 insulin like growth factor (IGF-1) in peripheral blood and at the same time can cause abnormal expression and overexpression of its receptors [4]. IGF-1 itself is a multifunctional growth factor that can promote the proliferation and differentiation of colorectal epithelial cells and regulate cell metabolism. When IGF-1 and its receptors are overexpressed, they bind to each other to activate tyrosine kinase receptor, participate in cell proliferation and differentiation through phosphatidylinositol3-kinase (PI3K)/serine-threonine kinase(AKT) pathway and mitogen-activated protein kinase (MAPK)/Ras pathway, and play a carcinogenic role [12]. Leptin is a protein hormone that is secreted by adipocytes and can promote the proliferation of colon cancer cell HCT-116 through the PI3K/AKT/mammalian target of rapamycin (mTOR) signal transduction pathway and simultaneously can inhibit its apoptosis [13].

The results of this study demonstrated that there were more elderly CRC patients (≥60 years old) than young and middle-aged CRC patients (<60 years old) in the MS group, and the proportion of elderly patients in the MS group was higher than that in the non-MS group. Previous studies have proved that the incidence of MS at the age of ≥50 years in the CRC group was significantly higher

Table 2. Comparison between hypertensive and non-hypertensive patients in the non-MS group

	Hypertension (n=467) *n (%)*	*Non-hypertension (n=985)* *n (%)*	*p value*
Histological grade			0.238
I	14 (3.00)	24 (2.44)	
II	289 (61.88)	581 (58.98)	
III	162 (34.69)	360 (36.55)	
IV	2 (0.43)	20 (2.03)	
Metastasis			0.514
No metastasis	267 (57.17)	549 (55.74)	
Only lymph node metastasis	165 (35.33)	355 (36.04)	
Only single distant metastasis	13 (2.78)	22 (2.23)	
Multiple metastases	22 (4.71)	59 (5.99)	
Infiltration depth			0.059
Submucosa	60 (12.85)	81 (8.22)	
Intrinsic muscularis	88 (18.84)	149 (15.13)	
Slurry layer	137 (29.34)	358 (36.35)	
Whole layer and surrounding fibrous fatty tissue	182 (38.97)	397 (40.30)	
Lesion location			0.637
Right colon	109 (23.34)	231 (23.45)	
Left colon	120 (25.70)	228 (23.15)	
Rectum	230 (49.25)	510 (51.78)	
Multiple sites	8 (1.71)	16 (1.62)	

Table 3. Comparison between diabetic and non-diabetic patients in the non-MS group

	Diabetes (n=137) *n (%)*	*Non-diabetes (n=1315)* *n (%)*	*p value*
Histological grade			0.344
I	7 (5.11)	31 (2.36)	
II	88 (64.23)	782 (59.47)	
III	40 (29.20)	482 (36.65)	
IV	2 (1.46)	20 (15.21)	
Metastasis			0.625
No metastasis	81 (59.12)	735 (55.89)	
Only lymph nodemetastasis	43 (31.39)	477 (36.27)	
Only single distantmetastasis	3 (2.19)	32 (2.43)	
Multiple metastases	10 (7.30)	71 (5.40)	
Infiltration depth			0.008
Submucosa	26 (18.98)	115 (8.75)	
Intrinsic muscularis	21 (15.33)	216 (16.43)	
Slurry layer	32 (23.36)	463 (35.21)	
Whole layer and surrounding fibrous fatty tissue	58 (42.34)	521 (39.62)	
Lesion location			0.739
Right colon	36 (26.28)	304 (23.12)	
Left colon	38 (27.74)	310 (23.57)	
Rectum	58 (42.34)	682 (51.86)	
Multiple sites	5 (3.65)	19 (1.44)	

Table 4. Comparison between patients with BMI ≥25kg/m² and BMI <25kg/m² in the non-MS group

	BMI≥25kg/m² (n=327) *n (%)*	*BMI<25kg/m² (n=1125)* *n (%)*	*p value*
Histological grade			0.742
I	14 (4.28)	24 (2.13)	
II	190 (58.10)	680 (60.44)	
III	116 (35.47)	406 (36.09)	
IV	7 (2.14)	15 (1.33)	
Metastasis			0.831
No metastasis	183 (55.96)	633 (56.27)	
Only lymph node metastasis	117 (35.78)	403 (35.82)	
Only single distant metastasis	10 (3.06)	25 (2.22)	
Multiple metastases	17 (5.20)	64 (5.69)	
Infiltration depth			0.065
Submucosa	42 (12.84)	99 (8.80)	
Intrinsic muscularis	71 (21.71)	166 (14.76)	
Slurry layer	102 (31.19)	393 (34.93)	
Whole layer and surrounding fibrous fatty tissue	112 (34.25)	467 (41.51)	
Lesion location			0.002
Right colon	46 (14.07)	294 (26.13)	
Left colon	81 (24.77)	267 (23.73)	
Rectum	194 (59.33)	546 (48.53)	
Multiple sites	6 (1.83)	18 (1.60)	

Table 5. Comparison between fatty liver patients and non-fatty liver patients in the non-MS group

	Fatty liver (n=136) *n (%)*	*Non-fatty liver (n=1316)* *n (%)*	*p value*
Histological grade			0.490
I	4 (2.94)	34 (2.58)	
II	86 (63.24)	784 (59.57)	
III	44 (32.35)	478 (36.32)	
IV	2 (1.47)	20 (1.52)	
Metastasis			0.268
No metastasis	65 (47.79)	751 (57.07)	
Only lymph node metastasis	58 (42.65)	462 (35.11)	
Only single distant metastasis	6 (4.41)	29 (2.20)	
Multiple metastases	7 (5.15)	74 (5.62)	
Infiltration depth			0.537
Submucosa	14 (10.29)	127 (9.65)	
Intrinsic muscularis	22 (16.18)	215 (16.34)	
Slurry layer	58 (42.65)	437 (33.21)	
Whole layer and surrounding fibrous fatty tissue	42 (30.88)	537 (40.81)	
Lesion location			0.015
Right colon	22 (16.18)	318 (24.16)	
Left colon	28 (20.59)	320 (24.32)	
Rectum	86 (63.24)	654 (49.70)	
Multiple sites	0 (0)	24 (1.82)	

than that in the no-tumor control group [9-11]. In our study, although the MS group had small sample size, it was similar to the age to the existing literature, making up for the error caused by the small sample size, which indirectly proved that this study still has certain reliability. Thus, it can be concluded that CRC patients with MS are relatively older. Therefore, it is suggested that elderly patients aged 60 years or above with MS should be alert to the occurrence of CRC, raise the risk awareness of the disease, and undergo colonoscopy timely, so as to receive early prevention and early treatment.

At present there is little literature on how hypertension affects the occurrence and development of CRC. In this study, there were no significant differences in histological grade and metastasis (including only lymph node metastasis, only single distant metastasis and multiple metastases), lesion location and infiltration depth between the hypertension and the non-hypertension group. According to the results of this study, hypertension has no significant effect on the severity and metastasis of CRC. In addition, the statistical results of this study revealed that there was a significant difference in age between the two groups, and CRC patients with hypertension were a little older than those without hypertension. It can also be suggested that older people with hypertension should be alert to the possibility of CRC.

IR, as the main link in the pathogenesis of type 2 diabetes, will directly or indirectly lead to hyperinsulinemia [4,7]. This study suggested that there was no significant difference in metastasis between the diabetic and the non-diabetic group. In terms of infiltration depth, this study showed that CRC in patients with diabetes was more likely to infiltrate into the whole layer and its surrounding fibrofatty tissue than that in patients without diabetes. The reason may be that diabetic patients are often associated with diabetic gastrointestinal motility disorders. The long-term retention of metabolic end-products in the intestine results in long-term action of toxins and carcinogens on colorectal mucosal cells, which are prone to malignant transformation and have a higher degree of infiltration. This study also showed that there was a significant difference in age between the diabetic and non-diabetic group, and CRC patients with diabetes were older than those without diabetes, suggesting that elderly people aged over 60 years with diabetes should pay attention to receiving timely colonoscopy in order to achieve early detection and therapeutic intervention.

BMI is clinically used to determine whether a patient is obese. A large number of studies have indicated that central obesity, namely abdominal obesity, is more closely associated with tumorigenesis [13,14]. There is little literature on the pathological manifestations and metastasis of obesity in patients with CRC. Data of this study showed that the lesions of CRC patients with BMI ≥25 kg/m^2 were mostly located in the left colon and rectum. CRC patients with BMI ≥25 kg/m^2 were diagnosed at lower age than those with BMI <25 kg/m^2. Therefore, we think it may be because the age of patients with obesity is getting younger, leading to early age of onset of CRC in patients with obesity. Therefore, it is recommended that obese patients should be alert to the occurrence of CRC, receive colonoscopy as early as possible, and regularly followed up.

According to clinical observations, more and more people have been diagnosed with fatty liver, and more than two-thirds of obese patients are complicated with NAFLD [5,6]. The subjects of this study were all with simple fatty liver disease, which belongs to NAFLD. Studies have suggested that the incidence of CRC in patients with NAFLD is significantly higher than that in patients without NAFLD. Whether fatty liver has an effect on the pathological manifestations and metastasis of CRC was also observed in this study. The results manifested that except for lesion location, there were no statistically significant differences in other comparisons between fatty liver group and non-fatty liver group. Considering that some of the diagnostic methods are B-ultrasound results, the diagnostic rate of this method is lower than that of abdominal CT, which will have an impact on the statistical results.

In summary, raising the risk awareness of MS patients and reducing the occurrence of MS and its components can not only reduce the incidence of CRC, but also reduce its pathological manifestations and affect its metastasis. The relationship of MS and its components with CRC should be further studied.

Conclusions

CRC patients complicated with MS, hypertension alone and diabetes alone are diagnosed at advanced age, mostly at old age. The lesion in CRC patients with BMI ≥25 kg/m^2 is often located in the left colon and rectum, while it is mostly located in the rectum in CRC patients with fatty liver. Except for the influence of diabetes on the infiltration depth of CRC lesions, MS and its components have no significant effects on the pathological manifestations and metastasis of CRC.

Conflict of interests

The authors declare no conflict of interests.

References

1. Kachur S, Morera R, De Schutter A, Lavie CJ. Cardiovascular risk in patients with prehypertension and the metabolic syndrome. Curr Hypertens Rep 2018;20:15.
2. Uzel M, Sahiner Z, Filik L. Non-alcoholic fatty liver disease, metabolic syndrome and gastric cancer: Single center experience. JBUON 2015;20:662.
3. Collins KH, Herzog W, MacDonald GZ et al. Obesity, metabolic syndrome and musculoskeletal disease: Common inflammatory pathways suggest a central role for loss of muscle integrity. Front Physiol 2018;9:112.
4. Spatola L, Ferraro PM, Gambaro G, Badalamenti S, Dauriz M. Metabolic syndrome and uric acid nephrolithiasis: Insulin resistance in focus. Metabolism 2018;83:225-33.
5. Kim D, Touros A, Kim WR. Nonalcoholic fatty liver disease and metabolic syndrome. Clin Liver Dis 2018;22:133-40.
6. Mitsuhashi K, Hashimoto Y, Hamaguchi M et al. Impact of fatty liver disease and metabolic syndrome on incident type 2 diabetes; A population based cohort study. Endocr J 2017;64:1105-14.
7. Zhang D, You Y, Zhang Z. Temporal characteristics of social support in colorectal cancer survivors during the first year post operation. JBUON 2017;22:882-7.
8. Farsad-Naeimi A, Alizadeh M, Esfahani A, Darvish AE. Effect of fisetin supplementation on inflammatory factors and matrix metalloproteinase enzymes in colorectal cancer patients. Food Funct 2018;9:2025-31.
9. Ulagnathan V, Kandiah M, Zalilah MS et al. Colorectal cancer and its association with the metabolic syndrome: A Malaysian multi-centric case-control study. Asian Pac J Cancer Prev 2012;13:3873-7.
10. Goulart A, Varejao A, Nogueira F et al. The influence of metabolic syndrome in the outcomes of colorectal cancer patients. Diabetes Metab Syndr 2017;11 (Suppl 2):S867-71.
11. Harlid S, Myte R, Van Guelpen B. The metabolic syndrome, inflammation, and colorectal cancer risk: An evaluation of large panels of plasma protein markers using repeated, prediagnostic samples. Mediators Inflamm 2017;2017:4803156.
12. Berger MD, Stintzing S, Heinemann V et al. Impact of genetic variations in the MAPK signaling pathway on outcome in metastatic colorectal cancer patients treated with first-line FOLFIRI and bevacizumab: Data from FIRE-3 and TRIBE trials. Ann Oncol 2017;28:2780-5.
13. Wang D, Chen J, Chen H et al. Leptin regulates proliferation and apoptosis of colorectal carcinoma though PI3K/Akt/mTOR signalling pathway. J Biosci 2012;37:91-101.
14. Phillips E, Horniblow RD, Poole V et al. A potential role for hepcidin in obesity-driven colorectal tumourigenesis. Oncol Rep 2018;39:392-400.