Association of Liver Steatosis with Colorectal Cancer and Adenoma in Patients with Metabolic Syndrome

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Abstract. *Aim: Metabolic syndrome has been identified as a risk factor for colorectal cancer and adenoma. The aim of our study was to assess the risk of colorectal cancer and adenoma in an adult Italian population with metabolic syndrome. Patients and Methods: Ninety patients with metabolic syndrome were prospectively compared against a matched population without the syndrome to assess the prevalence of colorectal adenoma. Another 1,500 patients undergoing screening colonoscopy were prospectively analyzed: 134 patients with metabolic syndrome and colorectal adenoma were compared against a group of 108 patients with colorectal adenoma without metabolic syndrome to assess the prevalence of cancer. The study was performed from January 2008 until December 2010. Data were analyzed from March to June 2011. Results: The prevalence of colorectal adenoma was twice as high in patients with metabolic syndrome. The incidence of cancer was higher in patients with colorectal adenoma and metabolic syndrome. Associated obesity and liver steatosis were the only factors with independent statistical value. Conclusion: Metabolic syndrome is a risk factor for adenoma and cancer degeneration when obesity is present. Associated liver steatosis is a significant risk factor for colorectal cancer.*

Obesity is associated with several metabolic abnormalities which represent risk factors for coronary heart disease, such as diabetes, hypercholesterolemia, and arterial hypertension. Obesity is also associated with an increased prevalence of cancer (1-6).

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Key Words: Colorectal cancer, colorectal polyps, metabolic syndrome, obesity.

In 2001 and 2004, the National Cholesterol Education Program Expert of the American Heart Association defined a constellation of metabolic cardiovascular risk factors as "Metabolic Syndrome" (MS) (7, 8). A patient with metabolic syndrome is classified as having at least three out of five alterations: i) arterial hypertension (systolic pressure >130 mmHg; diastolic >85 mmHg); ii) fasting blood glucose >100 mg/dl; iii) increased waist circumference (men >102 cm; women >88 cm; iv) increased levels of serum triglycerides (>150 mg/dl); v) decreased levels of serum high-density lipoproteins (HDL) (men <40 mg/dl; women <50 mg/dl). The aim of our study was i) to determine the prevalence of colorectal adenoma in patients with metabolic syndrome ii) to assess the risk of colorectal adenoma cancer degeneration in patients with metabolic syndrome and iii) to evaluate different risk factors for cancer degeneration.

Patients and Methods

Patients who had a family history of colorectal cancer were excluded from the study. Patients were seen for normal screening for colorectal polyps and cancer. Twenty percent of the patients had vague symptoms, including abdominal distension, periodic light abdominal pain, postprandial sense of fullness; 5% of the patients referred "blood in the stools". All patients underwent blood testing, including of fasting serum lipoproteins, tryglicerides, and glucose. Arterial blood pressure was determined. For each patient, the body mass index (BMI) was calculated, and the waist circumference measured. A BMI >27 kg/m^2 was used to define an obese person. All patients underwent liver ultrasound to determine the presence of steatosis. The study was performed from January 2008 until December 2010. Data were analyzed from March to June 2011.

Prevalence of colonic adenoma and cancer in patients with metabolic syndrome. In a prospective study, 90 patients, aged more than 50 years (mean age=67 years; 45 males, 45 females) with metabolic syndrome were prospectively evaluated to determine the prevalence of colorectal adenoma. They were compared against 90 patients, matched for age and sex, without metabolic syndrome. Table I shows some of the clinical characteristics of the patients in the two groups.

Risk of cancer de-generation in patients with metabolic syndrome. In a prospective study, all patients with metabolic syndrome

Table I. *Clinical characteristics of patients with and without metabolic syndrome who had screening colonoscopy.*

Characteristic	Metabolic syndrome N=90	No metabolic syndrome N=90	*p*-Value
Mean age, years	67	68	0.10
Male/female, n	45/45	48/42	0.20
Asymptomatic, n	80	78	0.20
Non-specific abdominal symptoms, n	20	21	0.10
Episodes of abdominal pain, n	10	9	0.20
Referred blood per rectum, n	5	6	0.10

Table II: *Risk factors for colorectal polyps and cancer in 90 patients with metabolic syndrome. Statistical significance for each single factor, multiple regression analysis-independent statistical significance.*

Factor	Polyps/ cancer	No polyps	*p*-Value
Arterial hypertension, n	30/55	11/35	0.10
Fasting blood glucose <100 mg/dl	25/48	16/42	0.10
Increased waist circumference, n	37/52	4/38	0.002
Increased serum triglycerides, n	35/47	6/33	0.010
Decreased level of HDL, n	20/46	21/44	0.10
Obese	33/49	8/41	0.02

HDL: High-density lipoprotein.

diagnosed with a colorectal adenoma or carcinoma in the time period from January 2008 to December 2010 were compared to a group of patients with the same diagnosis during the same period but without metabolic syndrome. For all patients included in the study, possible risk factors for colorectal adenoma and cancer were analyzed. The study was approved by the Hospital Ethics Committee, and all patients gave signed informed consent for the procedures. Overall, out of 1500 screened patients, 242 were discovered to have colorectal adenoma or cancer.

Statistical analysis. Paired Student's *t*-test and unpaired *t*-test were used to evaluate differences for single parameters. Multiple regression analysis was used to determine the specific value of each single risk factor. Differences were considered significant at a *p*-value of less than 0.05

Results

Prevalence of adenoma in patients with metabolic syndrome. Among the 90 patients with metabolic syndrome, 17% had three indicators of the syndrome, 55% four indicators, and the remaining 28% five indicators. The prevalence of colorectal adenoma was 46% (41/90). There were two cases of colorectal cancer (2/90). In the normal population, the prevalence of colorectal adenoma was 25%. This difference was statistically significant ($p<0.05$) Patients with more indicators of metabolic syndrome had a higher prevalence of colorectal polyps, however, when analyzing the weight of each single factor by multiple regression analysis, only obesity (BMI >27 kg/m^2) was an independent risk factor for colorectal polyps (Table II)

Risk of cancer de-generation in patients with metabolic syndrome. Out of 1,500 patients who underwent colonoscopy, 242 were found to have adenomas and/or colorectal cancer. Out of these 242 patients, 134 (55%) had metabolic syndrome; 69 of these 134 patients had three criteria for metabolic syndrome (51.5%), 43% had four criteria, and the remaining 16.5% had five criteria; 108 did not have metabolic syndrome. The two groups were similar for age (mean=67 years) and sex (males 60%, females 40%). Overall, 166 out of the 242 patients (69%) had only adenoma and 76 (31%) had colorectal cancer, associated or not with adenoma. In 108 patients without metabolic syndrome, the incidence of colorectal cancer was statistically lower than in the 134 patients with metabolic syndrome: 80 cases of adenoma (74%) and 28 (26%) of colorectal cancer, associated or not with polyps, versus 86 (64%) and 48 (36%), respectively (Table III).

Overall, there was a statistical significant difference ($p<0.05$) in the incidence of colorectal cancer in patients with compared with those without metabolic syndrome. The presence of five criteria was a significant risk factor for colorectal cancer. However, when we used multiple regression analysis, only obesity (BMI >27 kg/m^2) and the presence of liver steatosis at ultrasound were independent risk factors for colorectal cancer (Table IV)

Discussion

The prevalence of obesity has increased significantly in the past 30 years (9, 10). Many studies have reported an association between the prevalence of metabolic syndrome and colon polyps in North American and Asian populations (11-19). A similar trend is also evident for our study in Italy. The only independent risk factor for colorectal adenomas was an increased BMI. The prevalence of colorectal polyps was doubled in our study in obese patients compared to non-obese adults. In addition, the incidence of colorectal cancer was much higher in obese patients. This probably reflects the tendency for colorectal adenomas to degenerate in obese patients.

The underlying mechanisms linking obesity and colorectal adenoma and cancer are still a matter of debate. Theoretically many factors can explain this increased risk for colorectal adenoma and cancer: sedentary life style; chronic constipation often associated with obesity; fat food diet; a higher incidence of liver disease, such as steatosis, which can lead to altered metabolism of some growth factors and inflammatory

Table III: *Clinical characteristics of patients with and without metabolic syndrome who underwent screening colonoscopy and in whom colorectal adenoma or cancer was detected.*

	Metabolic syndrome N=134	No metabolic syndrome N=108	*p*-Value
Colorectal cancer, n	48	28	0.04
Adenoma, n	86	80	0.10
Mean age, years	67	67	0.10
Male/Female	70/64	63/45	0.10
Non-specific abdominal symptoms, n	30	25	0.09
Referred blood per rectum, n	28	26	0.09

Table IV: *Risk factors for colorectal cancer in 242 patients with adenoma or cancer with and without metabolic syndrome. Multiple regression analysis-independent statistical significance.*

Factor	Cancer	Only adenoma	*p*-Value
Obesity	55/76	48/166	0.040
Liver steatosis (ultrasound)	57/76	32/166	0.030

mediators implicated in tumour growth (20). Altered hormone balance has also been investigated (21). Insulin resistance and modifications in levels of adipocytokines seem to be of great importance. Other biological factors such as gut microbiota, and bile acids are also emerging (17, 22-24).

In our study, in 86 out of 134 patients with metabolic syndrome (64%), there was evidence of liver steatosis, and all these patients were obese and had colonic adenomas with/without cancer. Theoretically, it is possible that obesity leads to liver steatosis, with resulting inadequate deactivation of several growth factors and inflammatory mediators. These growth factors may promote adenoma formation and their degeneration in cancer. This unifying hypothesis could also explain the higher prevalence of other types of cancer in patients with obesity.

The results of our study indicate that obese patients are at higher risk for colorectal adenoma and cancer. Screening colonoscopy is indicated in asymptomatic patients before the age of 50 years, as recommended for the general population. A weight loss program can be beneficial in preventing colorectal polyp formation, especially in teens and young adulthood (25-27).

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Received December 9, 2014
Revised December 24, 2014
Accepted January 8, 2015