Is Metabolic Syndrome A Risk Factor for Colorectal Adenoma?

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Abstract

Background and Aims: **Epidemiologic studies provide evidence for a link between obesity or diabetes and the risk for colorectal cancer. However, there is a lack of information about the relationship between metabolic syndrome and colorectal adenoma. Therefore, we investigated whether metabolic syndrome is a risk factor for colorectal adenoma.**

Methods: **We did a study for consecutive subjects who underwent colonoscopy as a screening exam at the Center for Health Promotion, Samsung Medical Center, from March 2004 to December 2005. According to the modified ATP III criteria, metabolic syndrome was diagnosed. We classified a total of 2,531 subjects into the adenoma group (n = 731) and the control group (n = 1,800), including normal colonoscopic finding, nonpolyp benign lesions, or histologically confirmed hyperplastic polyp.**

Results: **The prevalence for metabolic syndrome was 17% in the adenoma group and 11% in the control group. On the multiple logistic regression analyses, metabolic syndrome was found to be associated with an increased risk of colorectal adenoma (odds ratio, 1.51; 95% confidence interval, 1.18-1.93). Also, waist circumference among the individual components of metabolic syndrome was an independent risk factor for colorectal adenoma. An increased risk for metabolic syndrome was more evident for proximal than distal colon, for multiple (≥3), and for advanced adenoma in the adenoma group.**

Conclusion: **Metabolic syndrome was associated with colorectal adenoma. Abdominal obesity of the individual components of metabolic syndrome was an important risk factor for colorectal adenoma.** (Cancer Epidemiol Biomarkers Prev 2007;16(8):1543–6)

Introduction

Metabolic syndrome is characterized by central obesity, impaired glucose tolerance, hypertension, low high-density lipoprotein cholesterol, and hypertriglyceridemia. This syndrome was introduced for the early detection and treatment of the patients with high risk of cardiovascular disease and diabetes. Researchers have speculated that cancer may share several risk factors with cardiovascular disease (1-5). Insulin resistance, which is considered a primary factor in the mechanisms of metabolic syndrome, is also known to raise the risk of cardiovascular disease and cancer, which are the leading causes of death worldwide (5, 6). These results suggest that the concept of metabolic syndrome is important to decrease the cancer-associated mortality as well as the mortality of cardiovascular disease and diabetes.

Colorectal cancer is one of the most common malignancies and it is one of the leading causes of cancer mortality in the world. Understanding the risk factors for colorectal cancer may guide the development of strategies targeted toward its prevention. Several clinical characteristics comprised in metabolic syndrome, including obesity, dyslipidemia, and impaired glucose tolerance, have been linked to an increased risk for colorectal cancer in several recent epidemiologic studies (7-10). However, not enough information exists about the relationship between metabolic syndrome and colorectal neoplasm to determine whether we should screen colorectal neoplasm in the patients with metabolic syndrome (11, 12).

Therefore, the present study aimed to systemically examine whether metabolic syndrome is a risk factor for colorectal adenoma.

Materials and Methods

Subjects. We did a study on a consecutive series of subjects who wanted and underwent colonoscopy for colorectal cancer screening at the Center for Health Promotion, Samsung Medical Center in Seoul, Korea, from March 2004 to December 2005. This study was approved by the institutional review board of Samsung Medical Center. The exclusion criteria were a history of colon disease, such as colitis, polyps, or cancer; prior colonic surgery or colon polypectomy; a colonic examination (sigmoidoscopy, colonoscopy or barium enema) within the previous 5 years; and a medical history of severe liver, lung, renal, hematologic, or connective tissue disorders and other malignancies.

A total of 3,584 patients were screened. Of these, 367 refused to participate in the survey or they did not complete all phases of the study including incomplete colonoscopies (n = 42); 686 were excluded because of a history of colectomy (n = 10) or colorectal polypectomy (n = 220), a colonic examination within the previous 5 years (n = 440), or malignant neoplasms (n = 16). As result, 2,531 subjects were finally included in this present investigation (1,945 men and 586 women with a mean age of 51.8 ± 7.9 years). The included subjects were divided into two groups according to their premalignant potential; the case group (n = 731, 635 men and 96 women with a mean age of 53.6 ± 7.6 years) had histologically confirmed colorectal adenoma including tubular, villous, or serrated adenoma, and the control group (n = 1,800, 1,300 men and 500 women with a

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Table 1. Univariate and multivariate analyses of the risk for colorectal adenoma by age, gender, smoking, alcohol, and metabolic syndrome

	Control (n = 1,800)	Case (n = 731)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P	OR (95% CI)	P
Age (y)						
<50	848 (47%)	239 (33%)	1		1	
≥50	852 (53%)	492 (67%)	1.90 (1.58-2.29)	<0.001	1.90 (1.58-2.29)	<0.001
Gender						
Female	500 (28%)	96 (13%)	1		1	
Male	1,300 (72%)	635 (87%)	2.47 (1.95-3.14)	<0.001	2.14 (1.65-2.77)	<0.001
Smoking status						
Nonsmoker	1,391 (77%)	508 (69%)	1		1	
Smoker	409 (23%)	223 (31%)	1.49 (1.23-1.81)	<0.001	1.32 (1.08-1.62)	0.007
Alcohol use						
No	936 (52%)	298 (41%)	1		1	
Yes	864 (48%)	433 (59%)	1.57 (1.32−1.87)	<0.001	1.20 (0.99−1.45)	0.06
Metabolic syndrome						
No	1,600 (89%)	606 (83%)	1		1	
Yes	200 (11%)	125 (17%)	1.65 (1.30−2.10)	<0.001	1.51 (1.18−1.93)	0.001

mean age of 51.0 ± 7.9 years) had normal colonoscopic findings (n = 1,416), nonpolyp benign lesions such as nonspecific colitis (n = 111), or histologically confirmed hyperplastic polyp (n = 273).

The data included smoking, alcohol consumption (>40 g/d), a medical history of hypertension, diabetes, and hyperlipidemia; this was all collected from a standardized questionnaire.

Based on the ATP III-WPRO (Regional Office for the Western Pacific Region of WHO) definition according to the WPRO WC criteria (13), metabolic syndrome was defined if three or more of the following criteria were satisfied: (*a*) abdominal obesity, waist circumference >90 cm in men and >80 cm in women; (*b*) hypertriglyceridemia, ≥150 mg/dL; (*c*) low high-density lipoprotein cholesterol, <40 mg/dL in men and <50 mg/dL in women; (*d*) high blood pressure, ≥130 mm Hg systolic or ≥85 mm Hg diastolic; and (*e*) high serum fasting glucose, ≥110 mg/dL.

Laboratory Assay and Measurement. The fasting glucose was measured by the hexokinase method (Roche Diagnostics) on the Hitachi 7600 automated chemistry analyzer (Hitachi). The triglyceride was determined with a commercially available enzymatic method (Roche Diagnostics) on the Hitachi 7600 automated chemistry analyzer (Hitachi). High-density lipoprotein cholesterol was measured by the polyanion-polymer/detergent method (Daiichi Pure Chemicals Co., Ltd.).

The waist circumference was measured at the high point of the iliac crest at minimal respiration.

Colonoscopy. We did colonoscopy that reached at least the cecum after bowel preparation with Colonlyte 4 liter; this was composed of polyethylene glycol 3,350.24 g, sodium bicarbonate 6.74 g, NaCl 5.86 g, sodium sulfate 22.74 g, and potassium chloride 2.97 g. We examined the colonoscopic features, including the location, size, number of adenomas, colonoscopic appearance, and incidence of advanced adenoma in the adenoma group. The location of the colorectal adenoma was divided into the proximal colon, including the cecum, ascending colon and transverse colon (at least one location for the multiple adenomas), and the distal colon, including the splenic flexure, descending colon, sigmoid colon, and rectum. The size of the adenomas was classified into <5, 5 to 9, and ≥10 mm (the largest size was used for multiple adenomas). The number of adenomas was classified into 1, 2, and ≥3 adenomas. The criterion of the colonoscopic appearance was classified into sessile or pedunculated according to the presence or absence of a stalk. Also, advanced adenoma was defined as ≥1 cm in estimated diameter, containing >25% villous features, and/or high-grade dysplasia.

Statistics. Statistical analysis was done using the χ^2 test for comparison of the discrete variables and the t test was used for comparison of the continuous variables. The continuous

Table 2. Risk of the individual components of metabolic syndrome for colorectal adenoma

	Control (n = 1,800)	Case (n = 731)	OR (95% CI)*	P	OR (95% CI)†	P	OR (95% CI)‡	P
Elevated BP								
(−)	1,501 (83%)	572 (78%)	1		1		1	
(+)	299 (17%)	159 (22%)	1.40 (1.13-1.73)	0.01	1.31 (1.05-1.63)	0.02	1.23 (0.98-1.54)	0.07
Increased waist circumference								
(−)	1,256 (70%)	431 (59%)	1		1		1	
(+)	544 (30%)	300 (41%)	1.61 (1.34-1.92)	<0.001	1.46 (1.22-1.75)	<0.001	1.39 (1.15-1.68)	0.001
Raised FBS								
(−)	1,588 (88%)	619 (85%)	1					
(+)	212 (12%)	112 (15%)	1.36 (1.06-1.74)	0.02	1.10 (0.86-1.42)	0.45	1.00 (0.77-1.30)	0.98
Hyper TG (mg/dL)								
(−)	1,208 (67%)	430 (59%)	1					
(+)	592 (33%)	301 (41%)	1.43 (1.20-1.71)	<0.001	1.27 (1.06-1.53)	0.01	1.16 (0.96-1.41)	0.13
Low HDL (mg/dL)								
(−)	1,537 (85%)	618 (84%)	1					
(+)	263 (15%)	113 (16%)	1.17 (0.91-1.50)	0.22	1.09 (0.84-1.42)	0.50	1.07 (0.84-1.36)	0.59

Abbreviations: BP, blood pressure; FBS, fasting blood sugar; TG, triglycerides; HDL, high-density lipoprotein.
*Unadjusted.
† Adjusted for age, gender, smoking and alcohol.
‡ Adjusted for age, gender, smoking, alcohol and other components of metabolic syndrome.

variables measured in this study were expressed as the mean ± SD. Multivariate analysis was done using logistic regression. To examine the risks of potential confounders including metabolic syndrome for colorectal adenoma, multivariate models included adjustment for age, gender, smoking, alcohol, and metabolic syndrome as the categorical factors. In the models to examine the associations between individual components of the metabolic syndrome and colorectal adenoma, adjustments for age, gender, smoking, alcohol, and other metabolic syndrome components were included. Also, in the models that examined colonoscopic factors that have influence on the presence of the metabolic syndrome in the colorectal adenoma group, adjustments for age, gender, smoking, and alcohol were included. For each variable, the odds ratio (OR) and 95% confidence interval (95% CI) were given. A two tailed P value of <0.05 was considered statistically significant.

Results

Among 2,531 subjects included finally, the univariate and multivariate analyses for the risks for colorectal adenoma among the clinical factors, including age, gender, a history of current smoking and alcohol use, and the presence of metabolic syndrome, were shown in Table 1. On the multiple logistic regression analyses, old age (≥50 years) and male gender were strongly associated with an increased risk for colorectal adenoma (OR, 1.90; 95% CI, 1.58-2.29 and OR, 2.14; 95% CI, 1.65-2.77, respectively). Also, current smoking was associated with an increased risk (OR, 1.32; 95% CI, 1.08-1.62). No difference was found for the current alcohol use. The prevalence rates for metabolic syndrome as defined by modified ATP III criteria were 17% in the cases and 11% in the controls. The adjusted OR for colorectal adenoma was significantly increased in the individuals with metabolic syndrome (OR, 1.51; 95% CI, 1.18-1.93).

When the individual components of metabolic syndrome were analyzed separately, only the waist circumference was significantly associated with age, gender, smoking, alcohol, and other covariate factors adjusted OR for colorectal adenoma (OR, 1.39; 95% CI, 1.15-1.68; Table 2).

The analyses conducted according to location, size, number of colorectal adenomas and being a case of advanced adenoma were shown in Table 3. A positive association with metabolic syndrome was observed almost exclusively for the proximally located adenomas rather than the distally located and multiple (≥3) adenomas (OR, 1.48; 95% CI, 1.02-2.19 and OR, 2.14; 95% CI, 1.34-3.41, respectively). Also, advanced adenoma was significantly associated with age, gender, smoking, and alcohol-adjusted OR for metabolic syndrome in the patients with colorectal adenomas (OR, 1.99; 95% CI, 1.41-3.46).

Discussion

Metabolic syndrome is becoming increasingly common because of the epidemic of obesity and sedentary lifestyles worldwide. Cardiovascular disease and diabetes are well-defined clinical entities with a high mortality rate and they require aggressive intervention. The importance of metabolic syndrome from a clinical and public health perspective will be greatest in its earlier stages, before the development of cardiovascular disease or diabetes (14).

Several hypotheses explain the mechanisms of carcinogenesis in obesity or diabetes through inflammation, oxidative stress, and insulin resistance (5). There are several studies that have provided evidence that obesity was associated with colorectal cancer. These studies showed a significant positive association between obesity and colorectal cancer; the effect was relatively modest, with an increased risk of about 1.5 to 3 times (1, 8, 15). Furthermore, obesity has consistently been more associated with colorectal cancer in men than in women, in premenopausal women but not postmenopausal women, and in the colon rather than in the rectum. A recent meta-analysis of six studies found a 3% increase (95% CI, 2-4%) in the risk of colorectal cancer per a 1 unit increase in the body mass index (16). Also, it is well documented that diabetes contributes to the mortality and incidence of colorectal cancer. In a large-scale prospective study on a Korean population, Jee et al. (4) reported that higher fasting blood sugar levels (140 mg/dL and above) increased the risk of all types of cancer by up to 1.29 times. Further, several large-scale prospective studies have provided evidence that diabetes was associated with colorectal cancer (17-20). Ahmed et al. (7) recently reported that there was a positive association between metabolic syndrome and colorectal cancer, especially in men but not in women in a 14-year multicenter prospective cohort study.

In this study, we focused on the association between metabolic syndrome and colorectal adenoma, which is a premalignant lesion that tends to develop into colorectal cancer via the traditional adenoma-carcinoma sequence. To our knowledge, only two previous studies have examined the relation between metabolic syndrome and colorectal adenoma (11, 12). One study by Wang et al. (11) showed that metabolic syndrome was associated with rectosigmoid adenoma and that the body mass index and hypertriglyceridemia of the

Table 3. Risk of colonoscopic factors in relation to the presence of the metabolic syndrome in the adenoma group

	MS + (n = 125)	MS − (n = 606)	OR (95% CI)*
Location			
Proximal colon	49 (39%)	296 (49%)	1
Distal colon	76 (61%)	310 (51%)	1.48 (1.02-2.19)
Size (mm)			
<5	59 (47%)	352 (58%)	1
5 ≤ 10	47 (38%)	203 (34%)	1.38 (0.91-2.10)
≥10	19 (15%)	51 (8%)	2.22 (1.23-4.03)
Number			
1	68 (54%)	378 (62%)	1
2	22 (18%)	137 (23%)	0.89 (0.53-1.50)
≥3	35 (28%)	91 (15%)	2.14 (1.34-3.41)
Appearance			
Sessile	112 (90%)	564 (93%)	1
Pedunculated	13 (10%)	42 (7%)	1.56 (0.81-3.00)
Advanced polyp			
No	105 (84%)	553 (91%)	1
Yes	20 (16%)	53 (9%)	1.99 (1.41-3.46)

*Adjusted for age, gender, smoking, and alcohol.

individual components of metabolic syndrome were significantly associated with the age- and sex-adjusted ORs of rectosigmoid adenoma (OR, 1.32; 95% CI, 1.05-1.66 and OR, 1.33; 95% CI, 1.09-1.63, respectively). That study had several important limitations in that only the adenomas at the rectosigmoid, not at the entire colon, were examined, and the body mass index, not the waist circumference, was measured; further, there was no data on lifestyle habits such as smoking and alcohol consumption, and on the psychosocial behaviors. Another study by Morita et al. (12) also showed that metabolic syndrome was associated with a moderately increased risk of colorectal adenoma with an age- and hospital-adjusted OR of 1.48 (95% CI, 1.13-1.93). An increased risk was more evident for the proximal colon adenomas than for the distal colon adenomas, and this was almost exclusively observed for large lesions (≥5 mm in diameter). Also, that study had several important limitations in that all of the study subjects were men, and any data on the lifestyle habits, such as smoking, alcohol consumption, and the psychosocial behaviors, were not collected.

Compared with these studies, our present study has methodologic advantages in that total colonoscopy was done for all of the defined population. Additionally, the lifestyle factors related to metabolic syndrome, including smoking and alcohol consumption, as well as age and gender, were examined. In this study, metabolic syndrome was associated with colonic precancerous lesions, and this is in agreement with the previous studies (11, 12). We also attempted to systemically address the relationship between colorectal adenoma and the various features of metabolic syndrome. Interestingly, we found that only waist circumference was found to be associated with the development of colon adenoma when the individual components of metabolic syndrome were analyzed separately on the multiple logistic regression analyses. *In vivo* or *in vitro*, there are several studies showing that abdominal obesity had a higher risk for colon cancer than body mass index, and it was even independent of body mass index (21-25). Abdominal obesity reflects visceral fat deposition, which is associated with insulin resistance and higher circulating levels of insulin growth factor-I. In fact, as was best described by Giorgino et al. (21), there are distinct differences between the functions of subcutaneous fat and visceral abdominal fat with regard to insulin. The insulin and insulin growth factor-I axes are major determinants of both proliferation and apoptosis; thus, they may influence carcinogenesis by means of increased cell proliferation and reduced apoptosis (26, 27). That women tend to accumulate less visceral abdominal fat with weight gain than men is one explanation for the gender differences in the relationship between the risk of colon cancer and obesity. This explanation is somewhat complicated by comparisons of postmenopausal and premenopausal women (27). However, increased serum fasting glucose was not associated with the development of colon adenoma in our study, which may therefore require further study.

In addition, the present study revealed that an increased risk for metabolic syndrome was more evident for proximal than distal colon, for multiple (≥3), and for advanced adenoma in the adenoma group.

In summary, the present cross-sectional study of Korean men and women showed that an increased risk of colorectal adenoma was associated with metabolic syndrome, and, particularly for an increased risk of incurring proximal lesions, multiple adenomas and advanced adenoma. Importantly, abdominal obesity, of all the individual metabolic syndrome components, independently increased the risk for colonic precancerous lesions. In conclusion, our study suggests that the metabolic syndrome can be considered an important entity with regard to the prevention of colorectal cancer and cardiovascular disease and diabetes, and we speculate that waist circumference may be the main component of the metabolic syndrome cluster driving the association between metabolic syndrome and colon cancer risk.

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