

Association of Visceral Fat Accumulation and Plasma Adiponectin with Colorectal Adenoma: Evidence for Participation of Insulin Resistance

Sayaka Otake,¹ Hiroaki Takeda,¹ Yasukuni Suzuki,¹ Tadahisa Fukui,¹ Shinichiro Watanabe,¹ Katsuyoshi Ishihama,¹ Takafumi Saito,¹ Hitoshi Togashi,¹ Tadashi Nakamura,² Yuji Matsuzawa,² and Sumio Kawata¹

Abstract Purpose: Colorectal carcinogenesis is thought to be related to abdominal obesity and insulin resistance. To investigate whether visceral fat accumulation contributes to colorectal carcinogenesis, we examined its accumulation and the levels of the adipose tissue–derived hormone adiponectin in Japanese patients with colorectal adenoma.

Experimental Design: Fifty-one consecutive Japanese patients ages ≥ 40 years and with colorectal adenoma were subjected to measurement of visceral fat area by computed tomography scanning and plasma adiponectin concentration. The patients also underwent the 75-g oral glucose tolerance test. Insulin resistance was calculated by the homeostasis metabolic assessment (HOMA-IR) method. The controls were 52 Japanese subjects ages ≥ 40 years and without colorectal polyp. Cigarette smokers and subjects who consumed alcohol (≥ 30 g ethanol/d) were excluded.

Results: The patients with colorectal adenoma showed significantly more visceral fat area and significantly less plasma adiponectin concentration in comparison with the controls [odds ratio (OR), 2.19; 95% confidence interval (95% CI), 1.47–3.28; $P < 0.001$ and OR, 0.24; 95% CI, 0.14–0.41; $P < 0.001$, respectively] by logistic regression analysis. HOMA-IR index was also associated with colorectal adenoma (OR 2.60; 95% CI, 1.20–5.64; $P = 0.040$). Visceral fat area and adiponectin were associated with adenoma number (1, 2, ≥ 3), the size of the largest adenoma (< 10 and ≥ 10 mm), and adenoma histology (tubular and tubulovillous/villous).

Conclusions: These results suggest an association of visceral fat accumulation and decreased plasma adiponectin concentration with colorectal adenoma in Japanese patients. This study may offer a new insight to understanding the relationship of colorectal carcinogenesis with abdominal obesity and insulin resistance.

A relationship between body mass index (BMI) and increased risk for colorectal cancer has been suggested, especially for males (1). Recent reports have shown that the risk of colorectal cancer is associated with abdominal obesity with hyperinsulinemia and insulin resistance (2, 3).

Intra-abdominal adipose tissue mass has been assessed by measuring visceral fat area (VFA, cm^2) by computed tomogra-

phy (CT) scanning at the umbilical level (4–6). The area of VFA on the CT scan was shown related to the waist-to-hip circumference ratio (7). Many reports have shown VFA association with insulin resistance, diabetes mellitus, dyslipidemia, hypertension, and coronary heart disease (4–9). However, there have been few studies addressing the association between measured values of VFA and colorectal adenoma and cancer.

The adipose tissue–derived peptide hormone adiponectin has been reported to correlate inversely with whole body adipose mass (10). A decrease in plasma adiponectin with visceral fat accumulation is associated with insulin resistance, diabetes mellitus, and coronary heart disease (11–13). Recently, a low plasma concentration of adiponectin has been thought to be associated with tissue inflammation (14–16) and cancer development (17, 18). However, there has been no report on the relationship of plasma adiponectin concentration with colorectal adenoma and cancer. To clarify the role of abdominal obesity and insulin resistance in colorectal carcinogenesis, we measured VFA and plasma adiponectin concentration in Japanese subjects with and without colorectal adenoma.

Authors' Affiliations: ¹Department of Gastroenterology, Faculty of Medicine, Yamagata University, Yamagata, Japan and ²Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Osaka, Japan Received 9/13/04; revised 11/24/04; accepted 12/7/04.

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Requests for reprints: Sumio Kawata, Department of Gastroenterology, Faculty of Medicine, Yamagata University, 2-2-2 Iida-nishi, Yamagata 990-9585, Japan. Phone: 81-23-628-5307; Fax: 81-23-628-5311; E-mail: kawata@med.id.yamagata-u.ac.jp.

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Patients and Methods

Patient selection. Fifty-one consecutive Japanese patients ages ≥ 40 years and with histologically diagnosed colorectal adenoma were enrolled in this study. The patients underwent total colonoscopy during a voluntary health check-up or because of occult fecal blood loss at the Yamagata University Hospital and hospitals affiliated with the Osaka University between January 2001 and December 2001. Patients with hyperplastic polyps, cigarette smokers, and subjects consuming alcohol (≥ 30 g ethanol/d) were excluded from this study. Also excluded were those with a history of colectomy, gastrectomy, or colorectal polypectomy and those under dietary or drug treatment for diabetes mellitus. Three of the 51 patients had rectal adenoma. The controls were 52 consecutive Japanese subjects ages ≥ 40 years and without colorectal polyp or inflammatory bowel diseases, who underwent total colonoscopy because of a voluntary health check-up or occult fecal blood loss during the same period and at the same hospitals, with the same exclusion criteria. The controls were drawn from the same population as the patients with colorectal adenoma. The response rates for agreed participation in this study were 91% for cases and 87% for controls.

This study protocol was approved from the Yamagata University Faculty of Medicine Ethical Committee. Written informed consent was obtained in advance from all subjects.

Assays. A 75-g oral glucose tolerance test was done after the subjects had fasted overnight. A Teflon catheter was inserted into the antecubital vein for blood sampling, and samples were obtained for plasma glucose and free insulin concentrations in the basal period and after an oral glucose load at 30-minute intervals for 180 minutes. The subjects were classified as normal, impaired glucose tolerance, or diabetes mellitus in accordance with the WHO criteria (19). Insulin resistance was calculated by the homeostatic metabolic assessment (HOMA-IR) method as follows: $\text{HOMA-IR} = \text{fasting plasma insulin} \times \text{fasting plasma glucose} / 405$, whereas insulin is expressed in microunits/mL and glucose in mg/d (20). Venous blood for assay of plasma concentration of adiponectin was drawn from all subjects after overnight fasting. Plasma samples were kept at -80°C for subsequent assay. The plasma concentration of adiponectin was determined with a sandwich ELISA system (adiponectin ELISA kit, Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) as previously reported (10). Body weight and height were recorded, and body mass index (BMI, kg/m^2) was used as a measure of obesity.

Measurement of visceral fat area. The intra-abdominal visceral fat area (VFA) was measured at the level of the umbilicus by CT scan according to a procedure previously described (21). The border of the intra-abdominal cavity was outlined on the CT image, and VFA was quantified using standard software. The CT measurements were made blinded to case status. The coefficient of variation of these measurements by a single observer was $<1.5\%$, and that of variation for day-to-day measurements was $<1\%$. All CT scans were carried out using a CT scanner (General Electric Co., Fairfield, CT) with the subjects in a supine position.

Statistics. Differences of age, gender, fasting glucose, and insulin concentration, oral glucose tolerance test status, HOMA-IR, BMI, VFA, and plasma adiponectin concentration between patients and controls were assessed by Wilcoxon rank sum test or χ^2 test. The relationship of VFA or plasma adiponectin with colorectal adenoma was determined using a logistic regression method (SAS Software Release 8.2, SAS Institute, Inc., Cary, NC) to obtain the odds ratio (OR) and 95% confidence interval (95% CI). Continuous variables were used for age, BMI, HOMA-IR, VFA, and plasma adiponectin concentration. The association of adenoma number with VFA or adiponectin was assessed by the nonparametric Jonckheere test. The association of other tumor characteristics such as the largest size of adenoma and histology of the adenoma with VFA or adiponectin was assessed by Wilcoxon rank sum test. $P < 0.05$ was considered statistically significant.

Results

Age was not significantly different between the patients (59 ± 7.3 years, mean \pm SD) with colorectal adenoma and the controls (58 ± 7.1 ; Wilcoxon rank sum test; Table 1). The patient group consisted of 35 males and 16 females, whereas the control group had 34 males and 18 females. No difference in gender was observed between the patients and the controls (χ^2 test). Fasting plasma glucose concentration was not different between the two groups. Fasting insulin concentration was not significantly different between the two groups, although it tended to be higher in patients with colorectal adenoma (8.5 ± 2.3 microunits/mL) than in controls (6.1 ± 1.8 ; $P = 0.11$). Oral glucose tolerance test status was also not different between the two groups (normal/impaired glucose

Table 1. Baseline characteristics of Japanese patients with colorectal adenoma and controls (Wilcoxon rank sum test or χ^2 test)

Variable	Patients with adenoma (n = 51), \pm SD	Controls (n = 52)	P
Age (y)	59 ± 7.3	58 ± 7.1	>0.2
Gender			
Male	35	34	>0.2
Female	16	18	
Fasting glucose (mg/d)	105 ± 21	91.9 ± 18.9	>0.2
Fasting insulin (microunits/mL)	8.5 ± 2.3	6.1 ± 1.8	0.11
HOMA-IR	2.2 ± 0.7	1.4 ± 0.5	0.032
OGTT			
Normal	28	36	>0.2
IGT	14	11	
DM	9	5	
BMI (kg/m^2)	23.6 ± 2.9	22.8 ± 2.6	0.14
VFA (cm^2)	98.9 ± 36.3	66.6 ± 29.5	<0.001
Adiponectin ($\mu\text{g}/\text{mL}$)	7.0 ± 2.6	10.6 ± 2.5	<0.001

Abbreviations: OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance; DM, diabetes mellitus.

tolerance/diabetes mellitus were 28:14:9 in patients and 36:11:5 in controls; χ^2 test). However, HOMA-IR index was significantly higher in the patient than in controls (2.2 ± 0.7 versus 1.4 ± 0.5 ; $P = 0.032$). BMI was not significantly different between the patients (23.6 ± 2.9) with colorectal adenoma and the controls (22.8 ± 2.6), although there was a tendency to be higher in the patient group ($P = 0.14$).

The mean of VFA was $98.9 \pm 36.3 \text{ cm}^2$ in patients with colorectal adenoma, whereas it was $66.6 \pm 29.5 \text{ cm}^2$ in controls (Fig. 1). This indicated significant accumulation of visceral adipose tissue in patients with colorectal adenoma ($P < 0.001$; Wilcoxon rank sum test). In addition, the mean of plasma adiponectin was $7.0 \pm 2.6 \text{ }\mu\text{g/mL}$ in patients, whereas it was 10.6 ± 2.5 in controls, indicating that plasma adiponectin concentration was significantly lower in patients with colorectal adenoma ($P < 0.001$). BMI, VFA, and plasma adiponectin showed high correlation with each other (BMI versus VFA, Pearson's correlation coefficient $r = 0.683$, $P < 0.001$; BMI versus adiponectin, $r = -0.600$, $P < 0.001$; VFA versus adiponectin $r = -0.677$, $P < 0.001$).

The numbers of adenomas were 1 in 23 patients, 2 in 13, and ≥ 3 in 15. The size of the largest adenoma was $< 10 \text{ mm}$ in 41 patients and $\geq 10 \text{ mm}$ in 10 patients. The histology was that of tubular adenoma in 44 patients, tubulovillous in five patients, and villous in two patients.

Logistic regression analysis showed that both VFA and plasma adiponectin concentration were significantly associated with colorectal adenoma (OR, 2.19; 95% CI, 1.47-3.28; $P < 0.001$ and OR, 0.24; 95% CI, 0.14-0.41; $P < 0.001$, respectively; Table 2). HOMA-IR index was also associated with colorectal adenoma (OR, 2.60; 95% CI, 1.20-5.64; $P = 0.040$). These observations suggested an association of insulin resistance with colorectal adenoma.

VFA and plasma adiponectin concentration were associated with tumor number ($P < 0.01$ and $P < 0.05$, respectively; Jonckheere test; Table 3). In addition, VFA and adiponectin were associated with the size of the largest adenoma ($P < 0.01$ and $P < 0.01$, respectively; Wilcoxon rank sum test) and the histology of the adenoma ($P < 0.01$ and $P < 0.05$, respectively; Wilcoxon rank sum test).

Table 2. Factors associated with colorectal adenoma in Japanese patients assessed by logistic regression analysis

Variable	Odds ratio (95% confidence interval)	<i>P</i>
Age (y)	1.00 (0.95-1.06)	> 0.2
Gender (male versus female)	1.16 (0.51-2.64)	> 0.2
BMI (kg/m^2)	1.11 (0.96-1.28)	0.16
HOMA-IR	2.60 (1.20-5.64)	0.040
IGT versus normal	1.64 (0.65-4.16)	> 0.2
DM versus normal	2.31 (0.70-7.68)	0.17
VFA (cm^2)	2.19 (1.47-3.28)	> 0.001
Adiponectin ($\mu\text{g}/\text{mL}$)	0.24 (0.14-0.41)	> 0.001

Abbreviations: IGT, impaired glucose tolerance; DM, diabetes mellitus.

Discussion

Abdominal obesity, which is known to correlate strongly with visceral fat accumulation (4, 6), has been linked to cardiovascular disease (22), diabetes mellitus (5, 23), and overall mortality (24). Data have suggested that abdominal obesity might also be associated with colon (2, 3), breast (25), and prostate (26) neoplasia. Epidemiologic studies have shown an association between waist circumference and waist-to-hip ratio and colon neoplasia (2, 3).

In this study, we examined whether VFA is associated with colorectal adenoma in Japanese patients. The results suggested that visceral fat accumulation is a risk factor of colon adenoma. To our knowledge, this is the first report to show an association between measured VFA and colorectal adenoma. On the other hand, BMI was not significantly associated with colorectal adenoma. Schoen et al. (2) reported that higher levels of waist-to-hip circumference, but not BMI, were significantly associated with colorectal cancer. These data suggest that visceral adipose

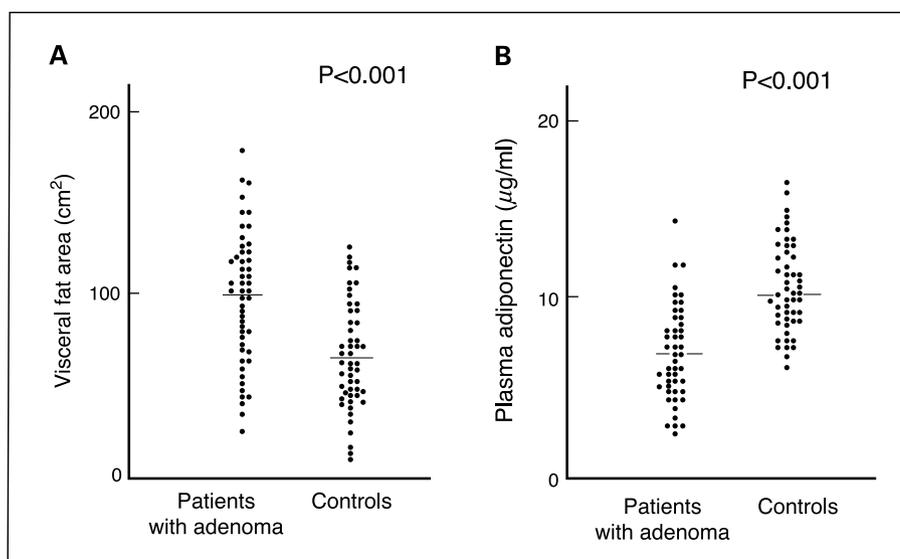


Fig. 1. A, comparison of VFA between Japanese patients with colorectal adenoma and controls in Japanese patients. VFA is significantly greater in the patients than in the controls ($P < 0.001$, Wilcoxon rank sum test). Bar, mean value of VFA in the patients and controls. B, comparison of plasma adiponectin concentration between Japanese patients with colorectal adenoma and controls. The adiponectin concentration is significantly lower in the patients than in the controls ($P < 0.001$, Wilcoxon rank sum test). Bar, mean value of plasma adiponectin concentration in the patients and controls.

Table 3. Association of adenoma number, size of the largest adenoma, and histology of adenoma with VFA or plasma adiponectin concentration in Japanese patients with colorectal adenoma

Variables	Adenoma number			P*	Size of the largest adenoma		P†	Histology of adenoma		
	1 (n = 23)	2 (n = 13)	≥3 (n = 15)		>10 mm (n = 41)	≤10 mm (n = 10)		T (n = 44)	TV/V (n = 7)	P†
VFA (cm ²)										
Median	80	110	118	<0.01	92	114	<0.01	97	138	<0.01
Minimum	35	26	51		26	98		26	98	
Maximum	146	161	179		154	179		154	179	
Adiponectin (μg/mL)										
Median	7.9	6.0	5.7	<0.05	7.5	5.1	<0.01	7.1	5.0	<0.05
Minimum	4.6	2.8	2.9		2.8	5.1		2.8	2.9	
Maximum	14.4	12.0	9.0		14.4	8.2		14.4	8.2	

Abbreviations: T, tubular; TV, tubulovillous; V, villous.

*Jonckheere test.

†Wilcoxon rank sum test.

tissue rather than whole body adipose tissue is associated with colorectal adenoma.

Plasma adiponectin concentration is known to decrease with obesity, especially in abdominal obesity in association with insulin resistance (27–32) and atherosclerosis (12, 33). In this study, we showed that decrease in plasma adiponectin concentration is a factor associated with the development of colorectal adenoma in Japanese patients. Low concentration of plasma adiponectin may be a risk factor of colorectal adenoma. Adiponectin also seems to participate in regulating inflammation and apoptosis possibly via inhibition of nuclear factor κ B signaling (14, 34). Recently, an association has been thought to exist between reduced adiponectin in blood and carcinogenesis (17, 18, 35). This study offers a new insight towards understanding the role of insulin resistance in colorectal carcinogenesis.

Logistic regression analysis showed that oral glucose tolerance test status, normal, impaired glucose tolerance, and diabetes mellitus did not show association with colorectal adenoma in this study. Several reports have shown that impaired glucose intolerance was associated with colorectal tumors (2, 36). These were large-scale studies for risks of colorectal cancer. Our findings may have been due to the small number of subjects. However, HOMA-IR index was associated with colorectal adenoma. Taken together with increased VFA and decreased plasma concentration of adiponectin, it seems that insulin resistance is associated with colorectal adenoma.

The number of colorectal adenomas and the size of the largest adenoma showed association with increased VFA and

decreased plasma adiponectin in this study. Histologic progression from tubular adenoma to tubulovillous/villous adenoma was also associated with increased VFA and decreased plasma adiponectin. Much epidemiologic evidence has suggested that the insulin-like growth factor-I (IGF-I) axis is associated with colorectal cancer risk (37). The Physician's Health Study showed that after adjustment for age, cigarette smoking, BMI, alcohol intake, and IGF-I binding protein-3 levels, men in the top quintile of circulating IGF-I had a relatively higher risk compared with those in the bottom quintile (38). Results from the Flexi-Scope trial also showed that high IGF-I and low IGFBP-3 levels increased the probability of high-risk adenomas, defined as at least one adenoma ≥ 1 cm in diameter of tubulovillous or villous morphology or with severe dysplasia or the presence of three or more adenomas (39). Further study is needed to examine whether there is a straightforward relationship between VFA and IGF-I and IGFBP-3.

In conclusion, our findings suggest that increased VFA and decreased concentration of plasma adiponectin are associated with the development of colon adenoma in Japanese patients. However, as this study was done with a small number of patients, a large-scale study is needed to clarify the association of visceral fat accumulation and adiponectin with the development of colon adenoma and cancer. Similar studies are also needed with other ethnic groups, including Caucasians and other Asians. Such research may warrant an intervention study on whether reduction of visceral fat accumulation and plasma adiponectin by weight loss and exercise (40) can prevent further development of colorectal adenoma.

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