Adiposity and Gastrointestinal Malignancy

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Key Words

Hyperlipidemia · Gastric cancer · Colorectal cancer · Adiponectin · Fat volume

Abstract

Recent epidemiologic studies have shown a positive association between obesity and certain cancers. Our retrospective studies show that hypertriglyceridemia is an independent risk factor for the development of colonic adenoma and nodal metastasis in early gastric and esophageal cancer in men. High-fat condition may be favorable for the growth of malignant cells. Serum level of adiponectin is reduced in patients with advanced gastric cancer, which may be associated with the positive link between adiposity and cancer. In early gastric cancer, patients with undifferentiated type have lower fat volume than those with differentiated type. Adiposity appears to be closely related with various aspects in pathophysiology of gastrointestinal malignancy.

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Introduction

The metabolic syndrome is one of the greatest concerns in developed countries. Abdominal obesity has been shown to be associated with increased risk not only for cardiovascular disease, diabetes and hypertension

[1–7], but also for malignant disease in various organs [8–11]. Since Lew and Garfinkel [12] first reported that being overweight and obesity increased the risk of mortality from cancer, many epidemiologic studies have shown a positive association between obesity and cancers in the endometrium [11, 13], breast [8, 14] and prostate [15] as well as in the gastrointestinal tract such as the colon [9, 16], gallbladder [17], gastric cardia [18, 19] and esophagus [20]. These results strongly suggest a mechanical link between adiposity and carcinogenesis. Here, we demonstrate some additional data to support this hypothesis in gastric and colorectal neoplasms.

Hyperlipidemia and Colorectal Neoplasms

Although previous data suggest a positive association between obesity and the development of colorectal cancer (CRC), it is unknown how adiposity has an impact on the multiple steps in colorectal carcinogenesis. Therefore, we retrospectively performed a large-scale retrospective study to analyze the correlation between the incidence of colorectal adenoma or carcinoma and the fasting serum levels of total cholesterol (TC) and triglycerides (TG) in 4,887 patients who underwent total colonoscopy for the screening of colon cancer [21]. As shown in figure 1, both TG and TC were significantly elevated in patients with adenomas compared with patients without any neoplas-

Fig. 1. Means $\pm$ SD of the serum levels of TC and TG of the patients with adenoma (n = 3,821), mucosal cancer (n = 386), invasive cancer (n = 110) and without any neoplastic lesions (n = 956). ** p < 0.01.

Table 1. Adjusted OR and 95% CI for tubular adenoma for a change of 1 SD in male or female patients

	TC			TG		
	OR	95% CI	p value	OR	95% CI	p value
Total (n = 3,787)						
Gross OR	1.3	1.21–1.39	<0.0001	1.64	1.48–1.82	<0.0001
Age-adjusted OR	1.01	0.93–1.09	0.79	1.34	1.21–1.48	<0.0001
Age-, gender- and TC- or TG-adjusted OR	1.04	0.96–1.13	0.334	1.13	1.01–1.09	0.013
Male (n = 2,997)						
Gross OR	1.32	1.19–1.47	<0.0001	1.35	1.19–1.56	<0.0001
Age-adjusted OR	1.09	0.98–1.23	0.13	1.24	1.09–1.43	0.0015
Age- and TC- or TG-adjusted OR	1.04	0.91–1.07	0.555	1.23	1.07–1.42	0.0041
Female (n = 1,890)						
Gross OR	1.49	1.34–1.65	<0.0001	1.42	1.25–1.64	<0.0001
Age-adjusted OR	1.08	0.96–1.21	0.21	1.04	0.92–1.17	0.56
Age- and TC- or TG-adjusted OR	1.06	0.95–1.02	0.29	1.02	0.91–1.16	0.7

Hypercholesterolemia and hypertriglyceridemia were defined as TC >220 mg/dl and TG >150 mg/dl, respectively.

tic lesions (TC 207.6 ± 29.5 vs. 199.5 ± 34.3 , n = 4,883, p < 0.001; TG 135.0 ± 82.2 vs. 108.7 ± 71.5 , n = 4,874, p < 0.001). The difference is significant in patients with tubular adenoma but not with villous or serrated adenoma (data not shown). Multiple logistic regression analysis considering age and gender revealed that TG was determined as an independent correlation factor in male but

not in female patients (table 1). The levels of TG in patients with invasive carcinoma did not show significant elevation compared to patients with adenoma. Those facts suggest that hypertriglyceridemia is an independent risk factor for the development of colonic adenoma in men, but not in females.

Table 2. Fasting serum levels of TC, TG and FBS in patients with colorectal adenoma, mucosal cancer and invasive cancer

	No adenoma (n = 92)	Adenoma (n = 682)	Mucosal cancer (n = 70)	Invasive cancer (n = 23)	p value
TC	203.90 ± 32.92	209.03 ± 27.19	208.07 ± 21.48	203.57 ± 25.52	0.8162
TG	111.59 ± 57.24	134.53 ± 68.31*	147.14 ± 81.14*	126.60 ± 47.11	0.0055
FBS	100.80 ± 29.49	105.79 ± 26.05	107.55 ± 26.75	121.86 ± 43.75 ⁺	0.0095

* p < 0.01 against no adenoma; ⁺ p < 0.001 against no adenoma, p < 0.01 against adenoma, p < 0.05 against mucosal cancer.

Table 3. OR of each variable for the development of adenoma, carcinoma and invasive carcinoma

Variable	p value	OR
Risk for adenoma in total patients (n = 867)		
Age	<0.001	2.18 (1.74–2.77)
Gender	<0.001	3.20 (1.92–5.42)
BMI	0.011	1.38 (1.08–1.78)
TG	0.443	1.12 (0.85–1.52)
FBS	0.295	0.87 (0.69–1.16)
Risk for carcinoma in patients with adenoma (n = 775)		
Age	<0.001	1.51 (1.20–1.93)
Gender	<0.001	3.33 (1.81–6.62)
BMI	0.236	1.16 (0.91–1.47)
TG	0.859	1.02 (0.81–1.26)
FBS	0.617	1.05 (0.85–1.27)
Risks for invasive carcinoma in patients with carcinoma (n = 93)		
Age	0.082	1.61 (0.96–2.85)
Gender	0.554	0.62 (0.13–3.44)
BMI	0.096	1.61 (0.93–2.93)
TG	0.121	0.55 (0.24–1.07)
FBS	0.027	1.74 (1.07–2.93)

Figures in parentheses are 95% CI. OR means ratio of male against female in gender, and ratios for a change of 1 SD in other variables.

Hyperglycemia and Colorectal Neoplasms

Among the patients, we could also evaluate serum levels of fasting blood sugar (FBS) in 867 patients [22]. The serum levels of FBS as well as TC and TG are expressed in table 2. TG and FBS, but not TC, showed positive association with the presence of colonic neoplasia. Patients with adenoma or carcinoma in situ showed significantly elevated TG level compared to those without adenoma ($p < 0.01$), while patients with invasive cancer showed a similar level of TG as those without adenoma. In contrast, FBS level was only slightly increased in patients

with adenoma or carcinoma in situ ($p > 0.05$), whereas it was markedly elevated in patients with invasive cancer compared to those without invasive cancer. As shown in table 3, multivariate logistic regression analysis revealed that age, gender and body mass index (BMI) were independent risk factors for adenoma in total patients. In patients with adenoma, age and gender, but not BMI, were independently associated with the increased risk for in situ carcinoma development. In those steps, neither TG nor FBS were identified as independent risk factors. However, in 93 patients with carcinoma lesions, only FBS showed significant association with the risk of invasive cancer with an OR of 1.74 ($p < 0.05$). TG showed a rather negative trend for invasive cancer with an OR of 0.55. These data suggest that hyperglycemia may correlate with the late step of the development of CRC.

Hyperlipidemia and Lymph Node Metastasis in Early Gastric Cancer

In contrast to CRC, serum TC and TG do not show significant differences between patients with early gastric cancer (EGC) and normal controls. Interestingly, however, we could detect the correlation between serum lipid levels and lymphatic metastasis in patients with EGC [23]. In 353 patients with EGC, 33 with positive lymph node metastasis showed significantly higher levels of TC and TG than the 320 patients without lymph node metastasis (fig. 2). The same tendency was observed in patients with early esophageal cancer, but not in patients with CRC (fig. 2).

Multivariate analysis demonstrates that hypertriglyceridemia, but not hypercholesterolemia, as well as submucosal invasion and lymphatic involvement were found to be independent risk factors for lymph node metastasis in 255 male patients (table 4). On the other hand, tumor size and undifferentiated type were independent factors, while depth and lymphatic invasion lost significance in

Fig. 2. Means $\pm$ SD of preoperative serum levels of TC and TG of EGC, CRC and esophageal cancer. In any patients, serum lipid levels were examined at early morning before breakfast on 2–6 days before operation after admission. * $p < 0.05$.

female patients (table 4). These data show that elevated serum TG levels might bring favorable circumstances for the development of lymph node metastasis in the early stage of gastric cancer (GC), at least in male patients.

Serum Adiponectin Levels and GC

The adipose tissue produces various growth factors or hormones called adipokines [24]. Adiponectin is one of the active adipokines which is related to the pathogenesis of diabetes through the modulation of glucose and fatty acid metabolism and insulin sensitivity in various stromal or epithelial cells [25, 26]. Interestingly, circulating levels of adiponectin have been reported to be inversely related with BMI and to be reduced in conditions of insulin resistance [25, 27]. Furthermore, we examined the serum adiponectin levels in patients with GC [28]. The plasma adiponectin levels were significantly decreased in patients with GC compared to healthy controls (fig. 3). Moreover, the adiponectin concentration tended to be reduced as the tumor stage increased (stage 1: 9.9 ± 6.9 μ g/ml; stage 2: 8.7 ± 5.5 μ g/ml; stage 3: 8.6 ± 4.1 μ g/ml; stage 4: 5.2 ± 6.2 μ g/ml), although BMI did not show any difference between the stages. Similar results have been reported in other malignancies, such as endometrial [29], breast [29, 30] and prostate [31, 32] cancers. This fact suggests that low plasma adiponectin levels are correlated with an increased risk for cancer, and raises the possibility that adiponectin has a potential role in cancer progression. In fact, many recent reports have suggested the antitumor effects of adiponectin both in vitro and in vivo

Table 4. Multivariate analysis of risk factors for lymph node metastasis in male and female EGC

	OR	95% CI	p value
Male			
Lymphatic invasion	4.21	1.68–10.56	0.0022
Submucosal involvement	21.09	2.32–191.33	0.0067
Size	1.26	0.39–4.03	0.6993
Hypercholesterolemia	3.59	0.84–15.21	0.0831
Hypertriglyceridemia	3.57	1.11–11.45	0.0327
Female			
Lymphatic invasion	3.42	0.54–21.59	0.1919
Submucosal involvement	2.58	0.51–13.12	0.2523
Size	15.71	1.80–136.71	0.0126
Undifferentiated type	10.03	1.03–97.28	0.0467

Factors identified in univariate analysis were included in multivariate analysis.

[33–36]. Since the circulating adiponectin levels are reduced in obesity, this adipokine may have an important protective role against carcinogenesis.

Fat Volume in Patients with EGC and CRC

Obesity is increased volume of the adipose tissue, and thus we next examined the fat volumes in patients with EGC and CRC. For subjective quantification, we examined the volume of visceral and subcutaneous fat in 1 slice of CT scan using the Fat Scan software (N2 System K.K.,

Fig. 3. Fasting plasma levels of adiponectin were determined in 75 GC patients and 52 healthy controls using the enzyme-linked immunosorbent assay. $p = 0.26$.

Fig. 4. VFA and SFA measured with the Fat Scan software in male (differentiated-type cancer: $n = 151$; undifferentiated-type cancer: $n = 23$) and female (differentiated-type cancer: $n = 24$; undifferentiated-type cancer: $n = 12$) patients with EGC. * $p < 0.05$.

Osaka, Japan) in 210 GC and 147 CRC patients [37]. As shown in table 5, BMI and total fat area (TFA) showed no significant difference between patients with GC and CRC cancer. Both BMI and TFA were the same in male and female patients. In contrast, visceral fat area (VFA) was significantly larger in male patients, while subcutaneous fat area (SFA) was larger in female patients, which is con-

Table 5. BMI and fat areas of patients with EGC and GC

Male (n = 276)	GC (n = 174)	CRC (n = 102)	p value
BMI	22.8 ± 2.9	22.9 ± 3.1	0.979
TFA, cm ²	199.6 ± 89.2	185.2 ± 85.4	0.175
VFA, cm ²	101.2 ± 52.7	91.9 ± 51.9	0.144
SFA, cm ²	98.4 ± 45.0	93.2 ± 43.9	0.24
VFA/SFA	1.07 ± 0.41	1.05 ± 0.53	0.434
Female (n = 81)	GC (n = 36)	CRC (n = 45)	p value
BMI	21.9 ± 3.3	21.4 ± 3.2	0.372
TFA, cm ²	208.7 ± 93.2	175.6 ± 82.6	0.081
VFA, cm ²	56.6 ± 36.8	50.2 ± 29.5	0.608
SFA, cm ²	152.1 ± 64.6	125.4 ± 60.2	0.037*
VFA/SFA	0.43 ± 0.34	0.47 ± 0.42	0.464

Data are averages ± SD. * $p < 0.05$.

sistent with data of the general population without cancer [38]. However, when VFA and SFA were separately compared in each sex, both parameters showed mostly the same values. Interestingly, both parameters tended to be high in patients with GC compared with those with CRC, although the differences were not statistically significant, except for SFA in female patients.

Another interesting finding in this study is that the fat volumes in patients with GC were significantly different by their histological types. As shown in figure 4, in male patients, VFA was significantly smaller in undifferentiated than differentiated type. SFA also tended to be smaller in undifferentiated type ($p = 0.07$). The trend was more prominent in female patients. VFA ($p = 0.004$) and SFA ($p < 0.001$) were markedly smaller in patients with undifferentiated GC than in those with differentiated histology. Compared with the general Japanese population, fat areas are considered to be reduced in patients with undifferentiated GC. These facts suggest that reduced fat volume may be mechanically related with the development of undifferentiated but not differentiated GC. Furthermore, TFA, VFA and SFA did not show a significant difference between mucosal and submucosal cancer in patients with differentiated cancer, whereas those values tended to be lower in submucosal than in mucosal cancer in patients with undifferentiated GC. With these results, we can raise a possibility that reduced fat volume may be favorable for submucosal invasion of undifferentiated

GC. Another speculation is that undifferentiated but not differentiated GC may already have systemic effects, inducing a reduction of subcutaneous fat volumes in early stage.

Conclusion

Increased body weight is certainly associated with increased death rates for cancers at multiple specific sites including the gastrointestinal tract [39]. Our data on the patients with gastric and CRC are mostly consistent with these results. Hyperlipidemia may provide a favorable

circumstance for the growth of malignant cells. Adiponectin may be the key molecule to explain the positive link between adiposity and cancer. Restriction of energy intake may be another reasonable strategy to prevent GC and CRC in obese people.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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