JBUON 2014; 19(3): 681-685
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Post-treatment plasma omentin levels in patients with stage III colon carcinoma

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Summary

Purpose: *Gastrointestinal carcinomas are ~1.5-2-fold more prevalent in obese populations compared to non-obese ones. Possible factors playing an important role in the association between obesity and cancer include insulin, insulin like growth factor-I, sex steroids and adipocytokines. This study investigated the omentin levels, a novel adipocytokine, in patients with stage III colon carcinomas (CC).*

Methods: *The study investigated 45 patients with stage III CC who had been treated with surgery and adjuvant oxaliplatin, leucovorin and 5-fluorouracil chemotherapy. The study control group was composed of 35 healthy individuals.*

Results: *The median age of the CC and control groups was 62 (range 32-74) and 56 (range 43-71) years, respectively (p=0.206). There were no significant differences between the CC and control groups in terms of gender (p=0.218), body mass index (BMI) (p=0.218), fasting blood glucose (p=0.487), total cholesterol (TC) (p=0.521), low-density lipoprotein (LDL) (p=0.722), high-density lipoprotein (HDL) (p=0.078), triglycerides (TC) (p=0.698), hemoglobin (p=0.096) and creatinine levels (p=0.130). The median plasma omentin concentration was 618 pg/mL (range 151-758) in the CC group and 376 pg/mL (155-662) in the control group (p<0.001). No significant correlation was found between omentin and the other parameters examined in the CC group.*

Conclusion: *Omentin levels are significantly elevated in stage III CC patients treated with surgery and chemotherapy. This elevation was independent of the basic risk factors associated with elevated omentin levels. Future studies of the pathophysiological causes of omentin elevation may facilitate the evaluation of the interactions between CC and adipose tissue.*

Key words: *adipocytokine, colon carcinoma obesity, omentin, stage III*

Introduction

CC is the third most prevalent cancer in both males (following prostate and lung cancer) and females (following lung and breast cancer). It is also the third leading cause of cancer death among males (following lung and prostate cancer) and females (following lung and breast cancer) [1].

The incidence of CC has increased rapidly in developed countries, especially amongst populations adopting a Western-type diet [2,3]. Weight gain is an independent risk factor in the etiology of many types of cancer including gastrointestinal cancers. Gastrointestinal carcinomas are ~1.5-2-fold more prevalent in obese populations compared to non-obese ones [4].

Several factors may play an important role in the association between obesity and cancer, including insulin, insulin like growth factor-I, sex steroids and adipocytokines [5]. Similarly, obesity may interact with CC via the following mechanisms: chronic low-grade inflammation, hyperinsulinemia, and alterations in the concentrations of insulin-like growth factor and adipocytokines [6].

Recent studies have shown that rather than being an energy store, adipose tissue should be considered as an active endocrine organ, produc-

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Received: 21/01/2014; Accepted: 06/02/2014

ing important proteins and cytokines for lipid and starch metabolism [7,8]. Moreover, adipose-derived cytokines cause proliferation and growth in stromal and malignant tumor cells [9].

Omentin-1 is a 34-kDa adipocytokine that is secreted mainly from visceral adipose tissue rather than subcutaneous adipose tissue [10,11]. Obesity and insulin resistance are associated with a reduction in omentin levels, thus omentin levels may have a predictive role in obesity-related metabolic conditions and co-morbidities [12].

This study aimed to investigate the levels of omentin, a novel adipocytokine, in patients with stage III CC treated with surgery plus adjuvant chemotherapy.

Methods

In this prospective study, after diagnosis and surgical treatment patients with stage III (T1-4 N1-2 M0) CC received oxaliplatin (85 mg/m^2/day; day 1), folinic acid (200 mg/m^2/day; day 1) and 5-fluorouracil (400 mg/m^2/day; day 1) by i.v. bolus injection, followed by continuous infusion of 5-fluorouracil (1600 mg/m^2/day) for 48 hours (FOLFOX-4) for 6 cycles (cycle repetition every 14 days; two administrations were considered as one cyle) [13]. Patients were included in the study if their control assessment (including chest radiography, abdominal ultrasound and tumor markers) revealed no recurrence or metastasis 2 months after chemotherapy.

We ruled out patients with metastatic disease with contrast enhanced computed tomography and magnetic resonance imaging. Surgical treatment (standard segmental colectomy and regional lymphadenectomy) was performed in all patients after diagnosis. The disease was staged according to the 7th edition of the American Joint Committee on Cancer Staging Manual.

The study protocol was approved by the Abant Izzet Baysal University (Bolu,Turkey) Ethics Committee (ABU.0.20.05.04-050.01.04-15/2013). Written informed consent was obtained from all participants.

Patients with coronary artery disease, severe hypertension, diabetes mellitus and renal failure (serum creatinine >1.5 mg/dL) were excluded from study. Patients with rectal carcinoma were excluded because they also received radiotherapy.

Age and gender-matched control subjects were selected from apparently healthy subjects who visited the outpatient internal medicine clinics of Abant Izzet Baysal University Hospital for a routine checkup.

Anthropometric measurements obtained in this study included height, weight and BMI [BMI= weight (kg)/height^2 (m^2)].

Study participant blood samples were collected from an antecubital vein after overnight fasting. Blood samples were centrifuged within 15 min of collection at 3000 rpm for 10 min, and the plasma was transferred into polypropylene tubes and stored at –80°C until assayed. Fasting blood samples were obtained for analysis of glucose, TC, LDL, HDL, TG, creatinine and hemoglobin.

Omentin measurement

Omentin concentrations were determined by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol. Plasma omentin levels were determined using a commercial ELISA kit (Bio Vendor, Brno, Czech Republic). The linear range of the assay was 0.50–64.0 mg/L. The inter- and intra-assay coefficients of variation were 4.4% and 3.2%, respectively.

Statistics

The statistical analysis was performed using SPSS for Windows, version 20.0 (SPSS Inc, Chicago, IL). Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test or Shapiro-Wilk test) to determine whether or not they were normally distributed. Descriptive analyses included the mean and standard deviations for normally distributed variables. Analyses of normally distributed variables (age, hemoglobin, TC, LDL, and TG) were conducted using Student's t-test. Analyses of abnormally distributed variables were conducted with the Mann-Whitney U test and descriptive analyses were presented as medians (min-max). The Spearman's test was used for correlation analysis of variables when at least one of them was distributed abnormally or ordinally. The type one error level was set at 5% for statistical significance. A p-value of <0.05 was considered to indicate statistical significance.

Results

The study group consisted of 45 CC patients and 35 control individuals. The median age of the CC group was 62 years (range 32-74), and 56 years (range 43-71) for the control group (p=0.206). There were no differences in gender, BMI, glucose, TC, LDL, HDL, TG, hemoglobin and creatinine between the CC group and control group. The clinical characteristics of the subjects studied are shown in Table 1.

The median plasma omentin concentrations were 618 pg/mL (range 151-758) in the CC group and 376 pg/mL (range 155-662) in the control group (p<0.001) (Table 1 and Figure 1). There was no significant correlation between omentin levels and the other parameters in the CC group.

Discussion

The present study showed that omentin concentration increased in patients with chemother-

Table 1. Demographic and lab characteristics of the colorectal cancer and control groups

Characteristics	*Colon cancer group (N=45)*	*Control group (N=35)*	*p-value*
Age (years)*	62 (32-74)	56 (43-71)	0.206
Gender (M/F)	26 / 19	18 / 17	0.574
BMI (kg/m^2)*	27 (19-37)	27 (20-38)	0.218
Glucose*	79 (67-100)	80 (68-100)	0.487
TC (mg/dl)	199.5 ± 40.6	205.0 ± 34.6	0.521
LDL-C (mg/dl)	128.06± 33.1	125.3 ± 34.8	0.722
HDL-C (mg/dl)*	41 (13-70)	44 (26-90)	0.078
TG (mg/dl)	167.2 ± 64.6	161.8 ± 57.2	0.698
Creatinine (mg/dl)*	0.8 (0.54-1.17)	0.7 (0.55-1.10)	0.130
Haemoglobin	13.1 ± 1.9	13.7 ± 1.4	0.096
Omentin (pg/ml)*	618 (151-758)	376 (155-662)	<0.001

* Data of abnormally distributed variables were expressed as mean ± standard deviation and median (min-max).
For abbreviations see text

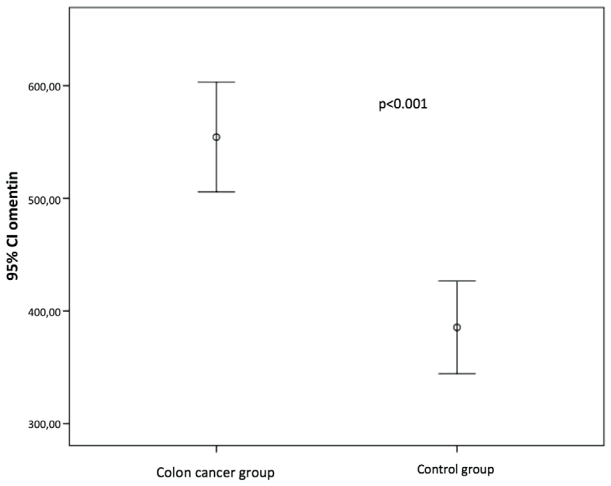

Figure 1. Plasma omentin levels in the colon carcinoma and control groups.

apy-treated stage III CC. The increase in omentin levels was independent of BMI, glucose and lipid parameters.

Recently, the role of many cytokines has been studied in CC development. Leptin is one example and has an important role in the neuroendocrine, reproductive and hematopoietic systems, as well as in influencing body weight [14]. Leptin levels decrease in CC patients and a reduction of leptin concentration has been found to be associated with CC development [15]. Another report revealed that adiponectin and resistin levels were lower in patients with CC compared to adenoma and control subjects, suggesting that these proteins might have an important role in colon carcinogenesis [16].

Otake et al. considered intraepithelial carcinoma and submucosal invasion as early stage CC, and muscularis propria invasion as advanced stage and showed that a decreased adiponectin level was the most important factor associated with early stage CC [17]. The authors concluded that males with lower levels of adiponectin had a higher risk of CC compared to those with elevated levels of adiponectin [18]. A decrease in adiponectin stimulates activation of PI3K/Akt signal pathway. This pathway activates in turn signals for cell survival, cell growth and cell cycle leading to carcinogenesis [19].

In another report, leptin, adiponectin, resistin and visfatin levels in CC patients were investigated, and the authors found that in contrast to leptin and adiponectin, resistin and visfatin levels were increased compared to controls. Moreover, stage progression was significantly correlated with resistin and visfatin levels and the authors concluded that those two biomarkers might be useful for determining CC malignant potential and stage progression [20]. These studies demonstrated that leptin and adiponectin decreased and resistin and visfatin increased in patients with CC.

A novel adipocytokine, omentin-1, is a galactose-binding lectin found in the goblet cells of the colonic mucosa. The metabolic effects of omentin-1 are similar to adiponectin and decreased omentin levels have been found to be inversely correlated with obesity [12,21,22]. Both omentin-1 and omentin-2 gene expression have been found to decrease with obesity and are highly correlated in visceral adipose tissue. Decreased omentin levels are associated with increasing obesity and insulin resistance. Therefore, omentin levels may be predictive of the metabolic consequences, or co-morbidities associated with obesity [12]. Although BMI was not significantly different between the two groups in this study, omentin levels were significantly increased in the CC group compared to the control group.

In accordance with the results presented here, it has been reported previously that omentin levels were significantly higher in patients with CC compared to controls. Although the authors did not exclude patients with diabetes mellitus, omentin levels were significantly increased compared to healthy subjects in that report. Fazeli et al. reported higher levels of omentin-1, visfatin, and vaspin in patients with CC, independent of measures of obesity. Those findings suggest that omentin-1, visfatin, and vaspin may play a role in the development of CC through mechanisms oth-

er than the indirect mechanisms recognized to be active between obesity and CC [23].

In another study the authors observed omentin in gastric carcinoma and found that omentin expression was correlated with the clinicopathological features of gastric carcinoma, indicating that it may be a prognostic factor in this disease [24].

Another study investigated the effects of omentin-1 on hepatocellular carcinoma and in particular the effects of omentin on HepG2 and HuH-7 hepatoma cells. Omentin-1 was found to have no effect on p53 mRNA levels in these cells. However, the bax/bcl-2 protein ratio was increased and the caspase-3 signaling pathway was activated. Omentin-1 triggered JNK signaling, but not p38 and ERK1/2 signaling pathways in HepG2 cells treated with omentin-1 [25]. The increase in omentin levels observed in our study may either be a consequence of reactive elevation in response to CC, or the increase in omentin may trigger CC development. However, we cannot speculate on this theory because we did not measure the pretreatment omentin levels of the study group.

In conclusion, omentin levels are significantly elevated in patients with stage III CC without diabetes mellitus who were treated with surgery and chemotherapy. Future studies of the pathophysiological causes of omentin elevation may be useful to evaluate the interactions between CC and adipose tissue.

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