UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 33: 135–142, 2014

Original paper
Originalni naučni rad

THE ROLE OF ADIPOCYTOKINES IN COLON CANCER AND ADENOMAS

ULOGA ADIPOCITOKINA U KANCERU I ADENOMIMA DEBELOG CREVA

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Summary

Background: Metabolic changes resulting from obesity, insulin insensitivity, and imbalances in hormones such as adiponectin, leptin, resistin, apelin and visfatin, which are derived from white adipose tissue-derived hormone, are directly linked to both colon cancer (CC) and inflammatory bowel diseases increasing tissue-derived risk. We conducted this study to evaluate the relationship between the circulating concentrations of adiponectin, leptin, resistin, apelin and visfatin and colon adenoma and CC.

Methods: Our study included 90 participants aged >18 years who were divided into three groups: colon cancer, adenoma and control. The serum concentrations of the investigated adipohormones were measured with ELISA in 30 patients with colon adenoma, 30 with CC and 30 controls with no colon pathology.

Results: Demographic, anthropometric, metabolic and hormonal parameters were also recorded. The group means were compared by using one-way analysis of variance (ANOVA). Dual comparisons between groups were analyzed with the Tukey test. Pearson correlation coefficient was used to determine the relation between continuous variables. Adiponectin and leptin levels in patients with adenomas ($p<0.000$; $p<0.000$, respectively) and CC ($p<0.000$; $p<0.000$, respectively) were lower than in controls. Apelin level in patients with CC ($p<0.000$; $p<0.000$, respectively) was lower than in patients with adenomas and in controls. Resistin and visfatin levels in patients with CC ($p<0.000$; $p<0.000$, respectively) were higher than in patients with adenomas and in controls.

Kratak sadržaj

Uvod: Metaboličke promene koje su posledica gojaznosti, neosetljivosti na insulin i poremećaja ravnoteže hormona kao što su adiponektin, leptin, rezistin, apelin i visfatin, koji potiču od hormona iz belog adipoznog tkiva, direktno su povezane sa rakom debelog creva (CC) kao i sa inflamatornim bolestima creva koje povećavaju rizik od raka debelog creva. Sproveli smo ovu studiju kako bismo istražili odnos između cirkulišućih koncentracija adiponektina, leptina, rezistina, apelina i visfatina, i adenoma i raka debelog creva.

Metode: Naša studija obuhvatila je 90 učesnika starih >18 godina koji su podeljeni u tri grupe: rak debelog creva, adenom i kontrolna grupa. Koncentracije ispitivanih adipohormona u serumu izmerene su pomoću ELISA kod 30 pacijenata sa adenomom debelog creva, 30 sa rakom debelog creva i 30 kontrolnih subjekata bez patoloških promena na debelom crevu.

Rezultati: Demografski, antropometrijski, metabolički i hormonski parametri takođe su beleženi. Proseci grupa upoređeni su pomoću analize ANOVA. Dvostruka poređenja između grupa izvedena su pomoću Tukijevog testa. Za određivanje odnosa između kontinuiranih varijabli upotrebljen je Pirsonov koeficijent korelacije. Nivoi adiponektina i leptina kod pacijenata sa adenomima ($p<0,000$; $p<0,000$) i CC ($p<0,000$; $p<0,000$) bili su niži nego kod kontrolnih subjekata. Nivo apelina kod pacijenata sa CC ($p<0,000$) bio je niži nego kod pacijenata sa adenomima i kontrolnih subjekata. Nivoi rezistina i visfatina kod pacijenata sa CC ($p<0,000$; $p<0,000$) bili su viši nego kod pacijenata sa adenomima i kontrolnih subjekata.

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Conclusions: We have concluded that adiponectin, leptin, resistin, apelin and visfatin levels may play an important role in colon carcinogenesis. We also assume that adiponectin and leptin may be associated with the risk of colon adenoma.

Keywords: adiponectin, apelin, visfatin, colon adenoma, colon cancer

Zaključak: Zaključujemo da nivoi adiponektina, leptina, rezistina, apelina i visfatina mogu igrati važnu ulogu u kancerogenezi debelog creva. Takođe pretpostavljamo da adiponektin i leptin mogu biti povezani sa rizikom za adenom debelog creva.

Ključne reči: adiponektin, apelin, visfatin, adenom debelog creva, rak debelog creva

Introduction

Among the causes of cancer deaths, colon cancer (CC) is one of the most common (1). Some risk factors such as feeding habits, lifestyle, obesity and total calorie intake and interactions between genetic and environmental factors have been found to play an important role in the development of CC (2). The increase in abdominal fat produces several factors and cytokines that play a role in the chronic inflammatory state related to obesity and following cancer risk. Metabolic changes resulting from obesity, insulin insensitivity, and imbalances in hormones such as adiponectin, leptin, resistin, apelin and visfatin, which are derived from white adipose tissue-derived hormones, are directly linked to both CC and inflammatory bowel diseases increasing CC risk (3).

The factors leading to ossification in adenomas are not completely understood; however, recent developments in our knowledge about cytokines and proinflammatory peptides may help explain this issue. Adenoma is the first stage of the development of CC and it can be observed as a mass of cells on the bowel wall (4).

Adiponectin, which is secreted by the adipose tissue, is a peptide hormone, and it is known to affect the metabolic process, protection from endothelial dysfunction, insulin sensitivity and weight loss (5). Adiponectin may prevent obesity-associated CC to a greater extent (6). Leptin, which is mainly produced by differentiated adipocytes, acts in the central nervous system through suppressing food intake and stimulating energy expenditure (7). Resistin, which is an insulin resistance-inducing factor, is the only signal molecule that is secreted from the adipocytes. It is mostly produced by monocytes and macrophages of peripheral blood. Resistin may act as a hormone which is related to insulin resistance-associated obesity; however, there is controversy among the results of the studies investigating the correlation between resistin and obesity (8).

Apelin, which was identified in the gastrointestinal tract, is known as an endogenous ligand for the G-protein-coupled APJ receptor. Apelin and APJ are also expressed in several tissues as well as the heart, lung, liver, kidney, brain, bone, gastrointestinal tract, adipose tissues and the skeletal muscle. Apelin regulates blood pressure, body fluid homeostasis, and cardiac contractility (9). Visfatin, which is secreted by visceral fat, is a new adipokine that imitates the effects of insulin. Visfatin has a significant role in various metabolic and stress responses and in the cellular energy metabolism such as Nampt (nicotinamide phosphoribosyl-transferase) (10).

There have been a few studies on the association between measured values of some adipocytokines, and CC and adenoma, but there is no research that has measured values of adiponectin, leptin, resistin, apelin and visfatin in the same study, according to our search on Pubmed. For this reason, we aimed to investigate the association of serum adiponectin, leptin, resistin, apelin and visfatin levels with CC and adenoma.

Materials and Methods

Study protocol

All study participants were recruited from consecutive patients who consulted the Gastroenterology Department of the Namık Kemal University Research and Practice Hospital in May 2011 and April 2012. The study included 90 participants aged >18 years who were divided into three groups: colon cancer, adenoma and control. The first group included: 30 colon cancer patients who had been diagnosed to have colon cancer by colonoscopy and biopsy. The second group included: 30 patients with adenoma located in the bowel, as diagnosed by colonoscopy. The last group included: 30 healthy people who had been diagnosed as free from colon cancer or adenoma by colonoscopy. Exclusion criteria included: treatment by chemotherapy, radiotherapy, or a major operation during the 6 months before recruitment; acute or chronic infection; history of eating disorders; or gastrectomy. Demographic, clinical and anthropometric data were collected upon recruitment. All pathology reports were reviewed, and data on tumor histology were recorded.

Biochemical analysis

Blood samples were obtained to determine glucose, lipid profile, protein, tumor markers, adiponectin, leptin, resistin, apelin and visfatin levels, after an overnight fast. The serum samples, obtained from the centrifugation, were then immediately frozen at –80 °C until further analysis of adipocytokines. Triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein

cholesterol (LDL-C) and tumor marker levels (CA-19-9 and CAE) were also measured within the same day. Colorimetric assays were used for serum glucose, protein, cholesterol, HDL and LDL levels on an autoanalyzer (Beckman) and a chemiluminometric immunoassay was used for the cancer markers (CA-19-9 and CAE) on an autoanalyzer (Roche).

The serum levels of adiponectin, leptin and resistin (AssayMax ELISA kit, USA) and apelin and visfatin (Phoenix ELISA kit, USA) were determined with enzyme-linked immunosorbent assay (ELISA) kits. Adiponectin, leptin, resistin, apelin and visfatin were measured in a sandwich-assay format using two specific and high affinity antibodies, one of which was biotinylated. As a reporter assay, streptavidin peroxidase conjugate and a chromogenic substrate were used. The minimum detectable level of adiponectin, leptin, resistin, apelin and visfatin is 0.7 ng/mL, 120 ng/mL, 0.2 ng/mL, 0.06 ng/mL and 3.12 ng/mL, respectively.

Ethical consideration

The protocol was approved by the Ethics Committee of Namık Kemal University Faculty of Medicine, and informed consent was obtained from all participants before their inclusion in the study.

Statistical analysis

PASW 18 Statistics for Windows was used to record and analyze data on the computer. All results were expressed as mean ± SD. First, the Shapiro–Wilk's test was used to test the normality assumption for each variable. The group means were compared by using one-way analysis of variance (ANOVA). Dual comparisons between groups were analyzed with the Tukey test. Pearson correlation coefficient was used to determine the relationship between continuous variables. We calculated the Pearson correlation between the investigated adipocytokines in the examined groups. The results were considered to be statistically significant at $p<0.05$.

Results

Demographic, anthropometric, metabolic, and hormonal parameters of the groups are given in *Table I*. No difference has been observed in BMI, glucose, cholesterol, HDL-C and LDL-C means among the patients with adenomas, CC and controls. Protein levels were significantly lower in CC when compared with controls. CA-19-9 and CEA levels were significantly higher in CC when compared with controls and adenomas.

Serum adiponectin levels were significantly lower ($p<0.000$) in the adenoma (4.64±0.64 μg/mL) and CC group (4.53±0.60 ng/mL) compared with the control group (6.01±0.81 ng/mL) (*Figure 1*). Leptin levels were significantly lower ($p<0.000$) in the adenoma (63.61±7.94 ng/mL) and CC group (58.90±6.74 ng/mL) compared with the control group (69.55±8.36 ng/mL) (*Figure 2*). Resistin levels (18.77±5.09 ng/mL) of the CC group were significantly higher ($p<0.000$) compared with both the control (13.36±6.36 μg/mL) and adenoma (13.40± 5.27 ng/mL) group (*Figure 3*). Apelin levels (1.63± 0.37 ng/mL) of the CC group were significantly lower compared with both the control (2.98± 0.66 ng/mL)

Table I Demographic, anthropometric, metabolic, and hormonal parameters (mean±SD).

	Control (mean±SD)	Adenoma (mean±SD)	Cancer (mean±SD)	p
Gender (M/F)	13/17	14/16	15/15	
Age (year)	54.7±10.0	60.2±1.4	61.4±1.5	0.075
BMI (kg/m^2)	28.6±5.4	28.9±2.7	26.4±4.0	0.066
Glucose (mmol/L)	5.94±1.17	5.49±1.00	5.72±1.55	0.477
Cholesterol (mmol/L)	5.33±1.42	5.18±0.96	4.84±1.45	0.358
Triglycerides (mmol/L)	1.40±0.29	1.42±0.61	1.24±0.62	0.397
HDL (mmol/L)	1.26±0.22	1.16±0.13	1.16±0.29	0.139
LDL (mmol/L)	3.59±1.05	3.44±0.80	3.13±1.28	0.270
Protein (g/L)	75±6	71±5	70±8a	0.027
CA-19-9 (U/mL)	5.34±3.89	5.78±3.17	23.62±22.92a,b	0.000
CEA (ng/mL)	2.23±1.70	1.91±1.03	5.27±4.74a,b	0.000

[a] $p<0.05$ compared to control group
[b] $p<0.05$ compared to polyp group

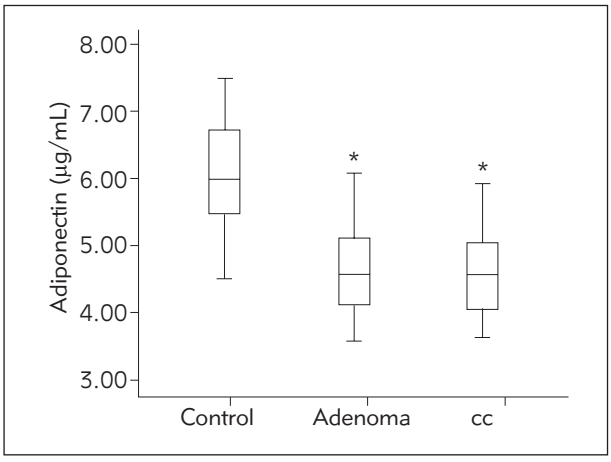

Figure 1 The serum levels of adiponectin of the patients with CC and adenoma (p<0.000).

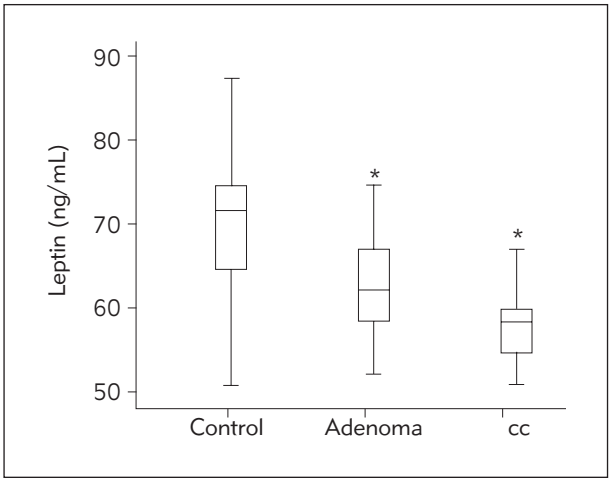

Figure 2 The serum levels of leptin of the patients with CC and adenoma (p<0.000).

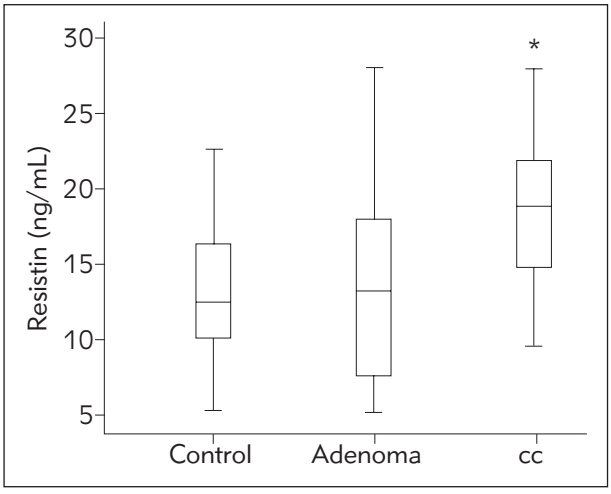

Figure 3 The serum levels of resistin of the patients with CC and adenoma (p<0.000).

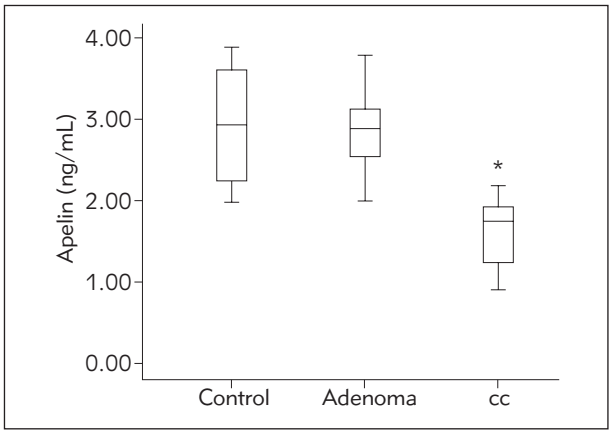

Figure 4 The serum levels of apelin of the patients with CC and adenoma (p<0.000).

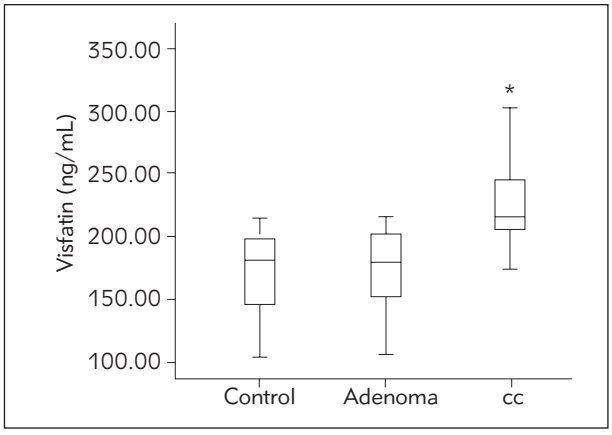

Figure 5 The serum levels of visfatin of the patients with CC and adenoma (p<0.000).

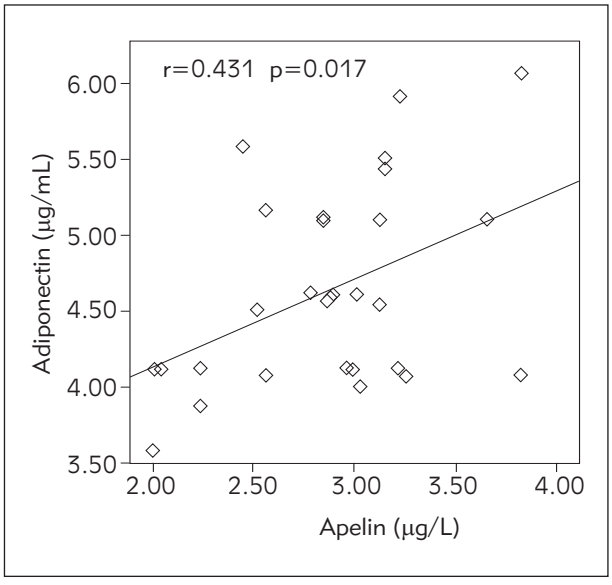

Figure 6 Correlation between serum adiponectin and apelin levels in patients with adenoma.

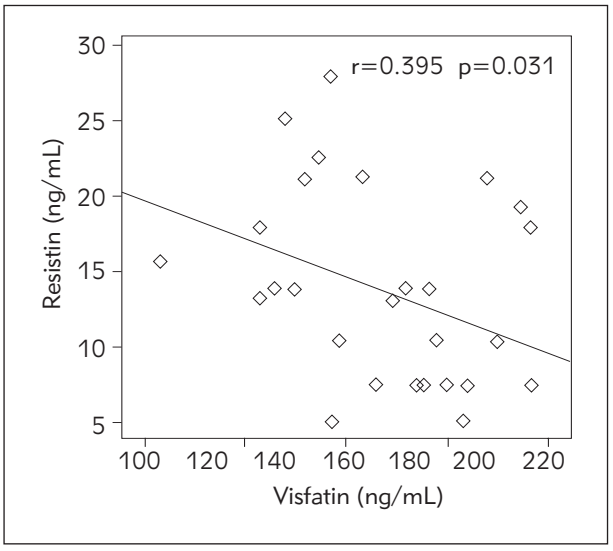

Figure 7 Correlation between serum resistin and visfatin levels in patients with adenoma.

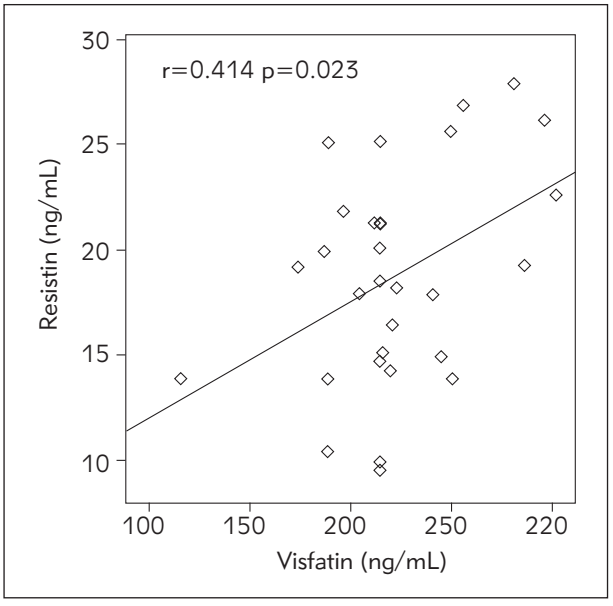

Figure 8 Correlation between serum resistin and visfatin levels in patients with CC.

and adenoma (2.88±0.48 ng/mL) group (p<0.000) (*Figure 4*). Visfatin levels (222.20± 38.33 ng/mL) of CC group were significantly higher compared with both control (171.80±32.04 ng/mL) and adenoma (175.60±30.06 ng/mL) group (p< 0.000) (*Figure 5*).

A significant positive correlation was found between adiponectin and apelin levels in patients with adenoma. A correlation was found between resistin and visfatin levels in patients with adenoma (*Figure 7*; r=–0.395, p<0.031). A significant positive correlation was found between resistin and visfatin levels in patients with CC (*Figure 8*; r=0.414, P<0.023).

Discussion

The main function of adipose tissue is to store energy. In addition, as an endocrine organ, it secretes a variety of adipocytokines like adiponectin, leptin, resistin, apelin and visfatin (8). In this study, we investigated relations among adiponectin, leptin, resistin, apelin and visfatin levels in a population of newly diagnosed, untreated CC and adenoma patients. Our results show complex interactions between these adipocytokines and CC and colon adenoma.

It is suggested that adiponectin is significantly associated with CC, preventive of the CC development, and lower levels of adiponectin lead to the development of CC. Adiponectin has an antiinflammatory and anticancerous activity (8). Previous research shows that adiponectin has a direct effect on carcinogenesis through inducing the activation of apoptotic enzymes in the caspase cascade decreasing tumor neovascularization, and inhibiting proliferation and myelomonocytic progenitors in smooth muscle cells (11). Moon et al. (12) claimed that adiponectin deficiency would significantly promote proliferative activity in colonic epithelial cells and, therefore, colon carcinogenesis would occur. Fujiawa et al. (13) also suggest that adiponectin inhibits the mTOR pathway through activating AMP-activated protein kinase (AMPK), which results in the suppression of cell proliferative activity. Kim et al. (14) observed that adiponectin repressed CC cell proliferation through the activation of adipoR1-and-R2-mediated AMPK. In our study, adiponectin levels in patients with CC were significantly lower compared with the control cases. There are several studies in literature that support our findings. Gonullu et al. (8) reported that serum adiponectin levels in patients with CC were significantly lower compared with control. Kim et al. (14) also showed that adiponectin overexpression significantly reduced proliferation of CC cells depending on the dose taken.

On the other hand, in Norwegian and Swedish populations, the circulating adiponectin levels were not linked to risk in nested case–control studies on colorectal cancer (15, 16).

In the present study, we observed that circulating adiponectin levels were significantly decreased in adenoma patients as compared to the control group. Erarslan et al. (2) reported that the decrease in circulating adiponectin levels is linked to the development of colorectal adenoma, and low levels of circulating adiponectin may be a risk factor for colorectal adenoma. Similarly, our data correspond with the observations of Kumor et al. (17) who found lower adiponectin serum levels in patients with adenoma compared with the control group. Nakajima et al. (18) reported an inverse correlation between the adiponectin level and colorectal adenoma. Furthermore, colon adenoma formation is promoted by the deficiency of adiponectin and colonic epithelial cell pro-

liferation is increased in animals fed a high-fat diet (13). In addition to these results, a significant decrease was observed in AMPK phosphorylation in intestinal epithelial cells of adiponectin-knockout mice compared with the control group (19).

Our results show that leptin serum levels were significantly lower in patients with CC compared with the control subjects. There is no consensus among studies on the serum leptin levels of patients with CC. Some studies report reduced levels of serum leptin in CC patients (17), while others indicate that increased serum leptin is associated with the incidence of CC (20). On the other hand, Tessitore et al. (21) showed that plasma leptin levels in CC were similar to controls. Similar to the findings of CC, we found significantly lower leptin levels in patients with colon adenoma compared with the control group. Kumor et al. (17) obtained lower serum leptin levels in patients with colorectal adenomas compared with control subjects, just as we did. They suggested that the low serum leptin level in colorectal adenoma patients could be linked to some causal factors of hypoleptinemia and some mechanisms which could not be explained clearly (17). The association between leptin levels and the risk of colorectal adenoma is still controversial. However, it has been suggested that leptin may be associated with the risk of colorectal adenomas in men (20).

In the present study, we observed that circulating resistin levels were significantly increased in CC patients as compared with the adenoma and control groups. Our results are in agreement with other studies which found higher levels of resistin in patients with CC (8). Salageana et al. (22) indicated that although serum resistin levels increased in CC patients, the serum levels of resistin and the tumor stage, localization or grade of differentiation were not correlated. In contrast, Wagsater et al. (23) found no significant difference in the levels of resistin in the plasma of CC patients in comparison with controls. The role of resistin in colorectal carcinogenesis has not been clarified yet. Existing data show that the serum resistin concentration might be a factor that contributes to increased CC risk. The activation of monocytes as a part of the inflammatory process may explain the increase in resistin levels in colorectal cancer patients (8). This may also explain the role of resistin in cancer, because chronic inflammation plays an important role in cancer pathogenesis and resistin is in close association with the inflammatory markers (24). We did not find a significant difference in serum resistin levels between the adenoma and control groups. There is insufficient data on colon adenoma in the present literature. To date, only Kumor et al. (17) studied resistin levels in patients with colorectal adenomas. They found that resistin levels increased significantly in patients with colorectal adenomas as compared with control cases.

Our results show that apelin levels in patients with CC were significantly lower when compared with control cases. To our best knowledge, there are no published data on apelin in CC and adenoma; however, the serum apelin concentration was measured in patients with other cancers and adenomas. Sorli et al. (25) suggested that the apelin gene expression was upregulated in a variety of human solid tumors. Berta et al. (26) hypothesized that apelin might promote non-small cell lung cancer growth via a stimulatory effect on blood capillaries. Kasai et al. (27) observed that apelin signaling regulated pathologic retinal vascularization in cooperation with vascular endothelial growth factor or fibroblast growth factor. According to previous reports, apelin expression is physiologically regulated by insulin, growth hormone, TNF-α and hypoxia in several tissues (28). Heo et al. (9) have demonstrated a link between apelin expression and poor prognosis in human non-small cell lung cancer and a correlation between strong apelin expression and tumor recurrence and poor prognosis. They suggested that apelin directly affected oral cancer proliferation and migration through an autocrine mechanism and APJ was expressed in oral cancer tissues and cell lines. Therefore, the multifaceted role of apelin in tumorigenesis may result from the differences in APJ expression in target cells (9). Yener et al. (29) found no significant differences between the circulating apelin levels of patients with non-functioning adrenal adenomas and control cases. These results show similarity with ours. Furthermore, we did not find any association between anthropometric characteristics, metabolic features and apelin. Various factors may be associated with these findings. First, the Apelin assay detected the apelin-12 fragment. However, apelin-13 and apelin-36 were important endogenous fragments detected in human tissues (28). Furthermore, similar anthropometric and metabolic features of the adenoma group and the healthy controls might cause similar levels of apelin in the groups.

In this study, we found that visfatin levels of patients with CC were significantly higher as compared with control and adenoma cases. Previous studies indicated that visfatin expression was associated with various malignancies such as esophageal, gastric, colorectal, breast and prostate cancers (10, 18). Endogenous visfatin was found to have increased in colorectal tumor tissue compared with non-neoplastic mucosa (18). Tilg et al. (30) suggest that visfatin, which is a new adipocytokine that can imitate insulin, directly interacts with the insulin receptor as the insulin-like growth factor receptor, which can then promote cancer cell proliferation. Visfatin contributes to the generation of NAD (nicotinamide adenine dinucleotide) biosynthesis and also affects cellular metabolism, cell life span and longevity, important signaling pathways and transcriptional regulation as well as TNF-α and IL-6 biosynthesis (10). A basic research study revealed that visfatin may contribute to

breast cancer etiopathogenesis by promoting cell proliferation through stimulating the cell cycle process, and by increasing the expression of genes significant in angiogenesis and metastasis (31). Visfatin upregulates cyclins and other cyclin-dependent kinases and thus activates the cell cycle process. In addition, it increases the synthesis of genes that play a significant role in tumor-related angiogenesis such as VEGF, in metastasis and tumor invasion such as matrix metalloproteases (31). Although the clinical correlations of visfatin with cancer have been rarely reported, Nakajima et al. (18) suggested that it could be considered to be a new and promising biomarker of colorectal cancer.

In conclusion, we have investigated the prospective use of serum adiponectin, leptin, resistin, apelin and visfatin levels in patients with CC and adenomas. Our findings suggest that these adipocytokines may be promising tumor markers for CC, and adiponectin and leptin may play a role as a biomarker of colon adenomas. Their levels could provide additional information and they are more useful in discriminating early stage cases. Whether the changes in these adipocytokine levels are the result and/or effects of CC or adenoma development should be investigated further, and the clarification of this causal association will certainly help explain the correlation between obesity and cancer. The results of our study suggest that resistin and visfatin may be good biomarkers of colon malignant potential independently from BMI.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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Received: December 29, 2012
Accepted: January 9, 2013