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.

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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. Sprovedi smo ovu studiju kako bismo istražili odnos između cirkulirajućih koncentracija adiponektina, leptina, rezistina, apelina i visfatinja, ađenoma i CC.

Metode: Naša studija obuhvatila je 90 učesnika starih >18 godina koji su podijeljeni u tri grupe: rak debelog creva, adenom i kontrolna grupa. Koncentracije ispitivanih adipohormona u serumu izmerene su pomoću ELISA kod 30 pacijenata sa adenomom, 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 ANOVA. Dvostruka poređenja između grupa izvedena su pomoću Tukijevega testa. Za određivanje odnosa između kontinuiranih varijabli upotrebili je Pearsonov 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 visfatinja kod pacijenata sa CC (p<0,000; p<0,000) bili su viši nego kod pacijenata sa adenomima i kontrolnih subjekata.
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.

Materials and Methods

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 and 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 who were diagnosed to have adenoma by colonoscopy. The last group included: 30 healthy people who had colonoscopy without any histological abnormalities during the 6 months before recruitment.

Blood samples were obtained to determine glucose, lipids profile, protein, tumor markers, adiponectin, leptin, resistin, apelin and visfatin levels, after an overnight fast. The serum samples, obtained from patients, were then immediately frozen at −80°C until further analysis of adipocytokines. 10 ml blood samples were obtained from the patients and blood pressure, body fluid homeostasis, and cardiovascular function were measured. All demographic, clinical and anthropometric data were recorded. 30 healthy people who had colonoscopy without any histological abnormalities during the 6 months before recruitment.

Biochemical analysis

Biochemical analysis was performed. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, low-density lipoprotein cholesterol (HDL-C), triglycerides, protein, glucose, C-reactive protein and tumor markers were measured in serum samples. Serum adiponectin, leptin, resistin, apelin and visfatin levels were measured in serum samples by enzyme-linked immunosorbent assay (ELISA).

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 and 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 who were diagnosed to have adenoma by colonoscopy. The last group included: 30 healthy people who had colonoscopy without any histological abnormalities during the 6 months before recruitment. 10 ml blood samples were obtained from the patients and blood pressure, body fluid homeostasis, and cardiovascular function were measured. All demographic, clinical and anthropometric data were recorded. 30 healthy people who had colonoscopy without any histological abnormalities during the 6 months before recruitment.
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 ng/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).

|                  | Control (mean±SD) | Adenoma (mean±SD) | Cancer (mean±SD) | p       |
|------------------|-------------------|-------------------|-----------------|---------|
| Gender (M/F)     | 13/17             | 14/16             | 15/15           | 0.075   |
| Age (year)       | 54.7±10.0         | 60.2±1.4          | 61.4±1.5        | 0.066   |
| BMI (kg/m²)      | 28.6±5.4          | 28.9±2.7          | 26.4±4.0        | 0.477   |
| 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±22.92ab   | 0.000   |
| CEA (ng/mL)      | 2.23±1.70         | 1.91±1.03         | 5.27±4.74ab     | 0.000   |

a p<0.05 compared to control group
b p<0.05 compared to polyp group

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

![Figure 7](image1.png) Correlation between serum resistin and visfatin levels in patients with adenoma.

![Figure 8](image2.png) Correlation between serum resistin and visfatin levels in patients with CC.
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 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
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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