



The relationship between serum adiponectin and resistin levels, insulin resistance and colorectal adenomas

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Nazlı Demir², Emel Ahışhali¹, Can Dolapçioğlu¹, Şerif Ercan³, Asuman Orçun Kaptanağası³, Reşat Dabak⁴, Nihal Yücel³, Mehmet Sargin⁴, Oya Uygur Bayramiçli⁵

¹Department of Gastroenterology, Dr. Lütfi Kırdar Kartal Education and Research Hospital, İstanbul, Turkey

²Department of Internal Medicine, Dr. Lütfi Kırdar Kartal Education and Research Hospital, İstanbul, Turkey

³Department of Biochemistry, Dr. Lütfi Kırdar Kartal Education and Research Hospital, İstanbul, Turkey

⁴Department of Family Medicine, Dr. Lütfi Kırdar Kartal Education and Research Hospital, İstanbul, Turkey

⁵Department of Gastroenterology, Maltepe University Faculty of Medicine, İstanbul, Turkey

ABSTRACT

Background/Aims: The relationship between adipocytokines and the development of colorectal cancer is well-documented. Our aim was to assess the relationship among serum adiponectin and resistin levels, insulin resistance, and colorectal adenoma to evaluate whether these parameters can be used as biomarkers to predict the development of colorectal adenoma.

Materials and Methods: This is a cross-sectional case-control study conducted in 32 patients with colorectal adenoma and 30 control subjects. Serum adiponectin and resistin levels, body mass index values, waist and hip circumferences and Homeostasis Model Assessment scores were measured.

Results: Resistin levels were slightly higher and adiponectin was slightly lower in patients with colorectal adenoma compared with controls; however, the differences in both parameters failed to reach statistical significance. The body mass index values and waist circumference of the patient group were significantly higher than controls ($p=0.003$ and $p=0.002$, respectively). Fasting serum insulin levels and Homeostasis Model Assessment scores of patients with colorectal adenoma were significantly higher than those of controls ($p=0.02$ and $p=0.02$, respectively). There was no relation between the number of colorectal adenomas and serum adiponectin or resistin levels.

Conclusion: Our data indicate that obesity and insulin resistance may contribute to the development of colorectal adenoma and that serum adiponectin levels and insulin resistance may not have a substantial predictive value for colorectal adenoma.

Keywords: Colorectal adenoma, adiponectin, resistin, insulin resistance, obesity

INTRODUCTION

Adipose tissue acts as a fat storage site as well as an endocrine organ that produces certain proteins, known as adipocytokines, which have autocrine, paracrine, and endocrine functions (1-3). An association between some of these proteins and the development of insulin resistance (IR) has been well-documented (3-5). Among the proteins released from the adipose tissue, resistin is increased in type 2 diabetes and is closely related with IR and obesity (2,3,5-8). In contrast, adiponectin is considered to possess antiatherogenic, antiinflammatory, and insulin sensitizing activities (8-16). Unlike other adipocytokines, adiponectin levels decrease in

the adipose tissue of obese and diabetic patients and low adiponectin levels were shown to be risk factors for the development of IR and diabetes (15,16). Therefore, endocrine dysfunction of adipose tissue has a significant contribution to the pathogenesis of obesity, IR, and diabetes.

Obesity is widely recognized as a risk factor for the development of colorectal cancer. The key factors that establish a causative link between obesity and colorectal cancer are IR and visceral lipoidosis (17-22). The relationship between adipocytokines released from adipose tissue and the development of colorectal cancer

Address for Correspondence: Emel Ahışhali, Department of Gastroenterology, Dr. Lütfi Kırdar Kartal Education and Research Hospital, İstanbul, Turkey E-mail: emelahishali@yahoo.com

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is well-documented (23-25). Low levels of adiponectin and high levels of resistin were considered as biomarkers to predict the development of colorectal cancer. Recent studies demonstrated a relationship between adiponectin and resistin levels and the development of colorectal adenoma (23,24,26,27). In the present study, we aimed to assess the relationship among serum adiponectin and resistin levels and IR and colorectal adenoma in order to evaluate whether these parameters can be used as indicators in predicting the development of colorectal adenoma by comparing data from patients with colorectal adenoma with healthy subjects, as documented through colonoscopy.

MATERIALS AND METHODS

Among the patients aged ≥ 18 years that underwent total colonoscopy in the Endoscopy Unit of Dr. Lütfi Kırdar Kartal Education and Research Hospital (734 colonoscopies performed in 2011), 32 patients that were histopathologically diagnosed as having colorectal adenoma following polypectomy were enrolled in this cross-sectional case-control study. Exclusion criteria included type 2 diabetes, IR, chronic liver deficiency, chronic renal deficiency, connective tissue disorder, inflammatory bowel disease, malignancy, or prior gastrointestinal system surgery. Patients were also excluded if they were detected to have colorectal cancer during colonoscopy. In addition, patients in whom complete examination (cecum or terminal ileum) was not achieved were also excluded. Thirty patients who had normal total colonoscopy served as controls. All participants in the control group had previously undergone colonoscopy for numerous indications: screening colonoscopy, abdominal pain, change of bowel movement habits, and iron deficiency anemia. The study protocol was approved by the Local Ethics Committee of Dr. Lütfi Kırdar Kartal Education and Research Hospital. Informed consent was obtained in advance from each of the patients and control subjects.

Demographic characteristics, body mass index (BMI), waist circumferences, hip circumferences, and physical examination findings of patients and control subjects were recorded. Blood samples were obtained for biochemical tests after 12 h fasting. Serum glucose and insulin levels were analyzed on the same day. Serum samples were also kept at -20°C until adiponectin and resistin levels could be analyzed. Serum glucose levels were measured using enzymatic glucose oxidase method in an autoanalyzer (Roche/Hitachi Modular D-P Systems, Mannheim, Germany). Serum insulin levels were examined with a paramagnetic-particle chemiluminescence immunoassay using the Access Immunoassay System (Beckman Coulter, Inc., Brea, CA, USA). IR was determined using the "Homeostasis Model Assessment" (HOMA) [fasting insulin ($\mu\text{U}/\text{mL}$) \times fasting glucose (mg/dL) / 405].

Serum adiponectin and resistin levels were quantified using a solid phase sandwich enzyme-linked immunosorbent assay through commercially available kits for human adiponectin

Table 1. Demographic characteristics, BMI values, waist and hip circumferences, fasting serum glucose and insulin levels, and HOMA scores of the patients with colorectal adenoma and the controls

	Adenoma group	Control group	p value
Age (years)	53.5 \pm 8.86	48.1 \pm 12.85	0.06
Female n (%)	12 (37.5%)	15 (50%)	0.33
Male n (%)	20 (62.5%)	15 (50%)	
Body mass index (kg/m^2)	29.14 \pm 3.92	26.06 \pm 3.80	0.003
Waist circumference (cm)	102.81 \pm 7.63	95 \pm 9.05	0.002
Hip circumference (cm)	106.09 \pm 7.27	103.4 \pm 8.06	0.17
Fasting glucose (mg/dL)	98.59 \pm 9.05	98.46 \pm 9.19	0.95
Fasting insulin ($\mu\text{U}/\text{mL}$)	12.05 \pm 11.96	6.93 \pm 3.13	0.02
HOMA scores	2.99 \pm 3.07	1.70 \pm 0.82	0.02

Results are expressed as mean \pm S.D. or n (%).

HOMA: homeostasis model assessment

and resistin (Kits for human adiponectin and resistin; eBioscience, San Diego, California, USA).

Data were presented as mean \pm SEM. Comparisons between patient and control groups were made using Student's t test and Chi-square test with a computer program (SPSS 16.0). A p value less than 0.05 was retained for significance.

RESULTS

Twenty (62.5%) out of 32 patients with colorectal adenoma were male and 12 (37.5%) were female. The mean age of the patient and control groups were 53.5 \pm 8.9 and 48.1 \pm 12.9 years, respectively. The number of males and females were equal among the 30 control subjects; 15 (50%) were male and 15 (50%) were female. No statistically significant difference was detected with respect to sex distribution and age between the patients with colorectal adenoma and control subjects. Demographic characteristics, BMI values, waist and hip circumference, fasting serum glucose and insulin levels and HOMA scores of the patients and the controls are summarized in Table 1.

While BMI and waist circumference values of the patient group were significantly higher compared with the controls ($p=0.003$ and $p=0.002$, respectively), there was no significant difference in hip circumference between the groups ($p=0.17$). Fasting serum insulin levels and HOMA scores of patients with colorectal adenoma were significantly higher than those of control subjects ($p=0.02$ and $p=0.02$, respectively). Fasting serum glucose levels were found to be similar in both groups.

Figure 1 shows serum resistin and adiponectin levels in both groups. Serum resistin levels were slightly higher in the patient group compared with the controls, but the difference was not significant (7154 \pm 3526 pg/mL vs. 6444 \pm 3172 pg/mL; $p=0.55$). The patient group tended to have slightly lower serum

adiponectin levels than those of controls; however, the difference failed to be statistically significant (8574 ± 6959 ng/mL vs. 9701 ± 7763 ng/mL; $p=0.40$).

We classified colorectal adenomas according to polyp diameter. Polyp size was identified as diminutive (≤ 5 mm), small (6-9 mm), or large (≥ 10 mm). Twenty five (78.1%) of all adenomas were diminutive, 3 (9.4%) were small, and 4 (12.5%) were large polyps. Thirty of the colorectal adenomas (93.8%) were tubular, and 2 (6.2%) were tubulovillous adenomas. All had low grade dysplasia. One of the 18 patients had a single adenoma, 10 had 2, 2 had 3, 1 had 5, and 1 had 6 adenomas. Characteristics of patients with single adenoma and those with ≥ 2 adenomas are presented in Table 2.

DISCUSSION

Although it has been demonstrated in epidemiological studies that obesity increases the possibility of colon cancer, the pathogenesis of this association is not yet completely understood (19-21). Obesity, particularly abdominal obesity, leads to hyperinsulinemia, IR, and type 2 diabetes. Current epidemiological data suggest that abdominal obesity increases the likelihood of colon cancer development more than high BMI does (21,26,28). Among the proposed mechanisms are changes in the metabolism of insulin, insulin-like growth factors, and endogenous hormones like adipocytokines. In addition, ethnicity and genetic characteristics are important in this relation (21,26).

Various studies have documented a relationship between adipocytokines released from adipose tissue and colorectal cancer carcinogenesis. In a case-control study, Nakajima et al. (23) examined the association of alterations in adipocytokine levels with carcinogenesis and the progression of colorectal cancer and adenoma. The authors concluded that resistin and visfatin levels could be useful for predicting the development of colorectal malignancy and staging the progression of colorectal cancer, independently from BMI. They also suggested that adiponectin levels might be a useful biomarker for colorectal adenomas. In another study by Kumor et al. (24), leptin, adiponectin, and resistin levels were measured in patients with colorectal cancer and adenomatous polyps. The authors suggested that serum levels of adiponectin and resistin might have a significant contribution in the carcinogenesis of colon cancer and that leptin may have a prognostic value independent of BMI. We investigated the relationship of adiponectin and resistin levels with colorectal adenomas. We compared 32 patients with colorectal adenoma with 30 controls with normal total colonoscopy. Although levels of adiponectin of the patient group were slightly lower compared with the controls, resistin was slightly higher in patients with adenoma when compared with the control subjects. However, contrary to the above mentioned literature data, statistical analysis revealed no significant difference of the variables in both groups. This result could be explained by the insufficient number of patients and genetic differences.

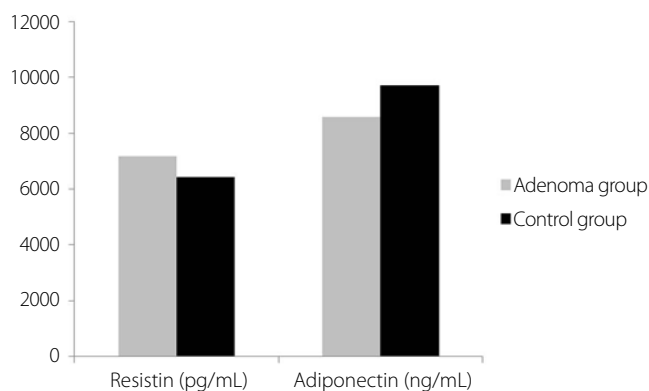


Figure 1. Serum resistin and adiponectin levels of the patients with colorectal adenoma and the controls.

Table 2. Characteristics of patients with single adenoma and ≥ 2 adenomas

	Number of colorectal adenoma:1 (n=18)	Number of colorectal adenomas ≥ 2 (n=14)	p value
Age (years)	53.27 \pm 8.91	53.92 \pm 9.13	0.84
Female (n)	10	2	0.01
Male (n)	8	12	
Body mass index (kg/m ²)	28.94 \pm 4.62	29.40 \pm 2.96	0.73
Waist circumference (cm)	102.72 \pm 8.92	102.92 \pm 5.88	0.93
Hip circumference (cm)	106.50 \pm 8.30	105.57 \pm 5.95	0.71
Fasting glucose (mg/dL)	98.50 \pm 8.30	98.71 \pm 10.26	0.95
Fasting insulin (μ U/mL)	14.58 \pm 14.84	8.80 \pm 5.76	0.14
HOMA scores	3.63 \pm 3.82	2.17 \pm 1.46	0.14
Resistin (pg/mL)	6607.44 \pm 3008.45	7857.85 \pm 4106.98	0.34
Adiponectin (ng/mL)	8918.33 \pm 8266.02	8132.85 \pm 5076.58	0.74

Results are expressed as mean \pm S.D. or n
HOMA: homeostasis model assessment

It is generally accepted that IR is an important contributor to the pathogenesis of metabolic syndrome. In an epidemiological study, metabolic syndrome was associated with increased risk of colorectal adenoma. The study also revealed that increased waist circumference, a component of metabolic syndrome, was an independent risk factor for colorectal adenoma (29). The association of visceral obesity and IR with colorectal adenoma was investigated in a cross-sectional case-control study. Multivariate analysis of data from that study revealed that visceral obesity was an independent risk factor of colorectal adenoma and that IR was associated with the presence of colorectal adenoma (28).

In an attempt to determine whether visceral fat accumulation contributes to colorectal cancer carcinogenesis, Otake et al. (26) examined its accumulation and adiponectin levels in Japa-

nese patients with colorectal adenoma aged over 40 years. The area of visceral fat, measured using computed tomography scanning (CT), was significantly higher in patients with colorectal adenoma, and a significantly lower plasma adiponectin concentration was observed in these patients when compared with controls. The authors also evaluated fasting plasma glucose and insulin concentrations, HOMA scores, and BMI values. Significantly higher HOMA scores were also noted in colorectal adenoma patients compared with the controls. The authors concluded that visceral fat accumulation and low serum levels of adiponectin are risk factors for colon adenoma. These findings suggest that abdominal obesity and IR may be associated with the development of colorectal adenoma. In our study, we measured waist circumference in order to assess visceral obesity. We found that BMI and waist circumference of colorectal adenoma patients were significantly higher than those of the controls. Although fasting glucose levels of both groups did not differ significantly, fasting insulin levels and HOMA scores in patients with colorectal adenoma were significantly higher than those of the control subjects.

Geographical regions, ethnicity, and genetic features may lead to variations in clinical manifestations of obesity and IR. Adipocytokines can also show likewise variations (7-9,26). Therefore, data in the literature from our country (Turkey) should also be taken into consideration. In a study conducted on Turkish patients, Gonullu et al. (25) investigated the associations among adiponectin, resistin, IR, and colorectal tumors. They found that HOMA scores and resistin levels were significantly higher and adiponectin levels were significantly lower in patients with colorectal cancer compared with controls. In the only local study that was conducted to understand the association of colorectal adenoma with adipocytokines, Erarlan et al. (27) examined the association of visceral fat accumulation and serum adiponectin levels with colorectal neoplasia, using CT. They observed that there was no significant difference in visceral fat accumulation between patients and controls. In addition, adiponectin level was shown to be significantly lower in colorectal carcinoma patients than in controls; however, there was no significant difference between patients with colorectal adenoma and controls with respect to adiponectin levels. Contrary to previous studies, we found no significant difference between adiponectin levels in colorectal adenoma and control groups, similar to Eraslan et al.'s results (27). We also found no difference between adiponectin and resistin levels of both groups. This may be explained by genetic and ethnic differences. Otake et al. (26) stated that similar studies in different ethnic groups were required to evaluate the link between visceral fat accumulation, adiponectin, and colorectal adenoma and cancer development.

The relationship between adenoma characteristics (number, size, and cytology) and adipocytokines was also evaluated in studies, but results were contradictory. Nakajima et al. (23) found an inverse correlation between adiponectin levels and

number of adenomas ($p=0.02$), but no relation with diameter of adenomas. In the Otake study (26), adiponectin level was significantly lower in patients with number of adenomas ≥ 3 adenomas, diameter ≥ 10 mm and tubulovillous/villous histology of the adenomas. In our study, there was no difference between the subgroups with a single adenoma and ≥ 2 adenomas according to the adiponectin and resistin levels, waist circumference, BMI, and IR. However, we were unable to compare adenoma diameter with adiponectin, resistin, and IR because 87.5% of the adenomas were < 10 mm and large adenomas were fewer in our study group. Similarly, Eraslan et al. (27) found no association between adiponectin levels and the number and histology of adenomas.

To conclude, our data indicate that obesity and IR may contribute to the development of colorectal adenoma, and yet, larger-scale studies encompassing subjects from a wide range of ethnic and genetic origins should be conducted to evaluate the association of adiponectin and resistin levels with colorectal adenoma characteristics.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dr. Lütfi Kırdar Kartal Education and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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