Serum Adiponectin Levels in Patients with Esophageal Cancer

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Received September 21, 2008; accepted November 15, 2008; published online December 30, 2008

Objective: The aim of the study was to investigate a possible relationship between serum levels of adiponectin and clinicopathological characteristics in esophageal cancer. This is the first report evaluating serum adiponectin levels in patients with esophageal cancer.

Methods: Sixty-two patients with esophageal cancer and thirty healthy subjects were included in the study. Adiponectin levels were determined by an enzyme-linked immunosorbent assay kit.

Results: The mean serum adiponectin level in the cancer group was significantly low compared with the adiponectin level in the healthy control group. Furthermore, adiponectin levels of the patients gradually decreased with increase in tumor stage. The patients with adenocarcinoma of the esophagus had significantly lower values of serum adiponectin than patients with squamous cell carcinoma.

Conclusion: We concluded that decreased circulating adiponectin levels may play a role in the progression and/or development of esophageal cancers. However, for clinical use of serum adiponectin in terms of early diagnosis and treatment, further studies should be performed.

Key words: adiponectin – esophageal adenocarcinoma – esophageal squamous cancer

INTRODUCTION

Adipose tissue is not simply an energy storage organ but also a secretory organ, producing a variety of bioactive molecules, including tumor necrosis factor-α, interleukin 6, angiotensinogen, plasminogen activator inhibitor type 1, resistin, leptin and adiponectin (1–3). These adipose tissue-derived factors play an important role in body homeostasis by influencing a variety of physiological processes, lipid and glucose metabolism, regulation of energy balance, angiogenesis and vascular remodeling, regulation of blood pressure and coagulation (2). Adiponectin, an adipose-specific plasma protein, acts as an anti-atherogenic hormone through the inhibition of proliferation of vascular smooth muscle cells and endothelial cells (1). Previous studies have revealed that adiponectin shows anti-inflammatory and anti-diabetic properties (4–6). Adiponectin may play an important role in the development and progression of some malignancies (3). Current studies indicated that blood adiponectin levels were inversely associated with the risk of endometrial, renal cell carcinoma, breast, colon and gastric cancer (7–11). However, the exact mechanism of anti-carcinogenic effects of adiponectin has been unclear.

Esophageal cancer is one of the most aggressive carcinomas of the gastrointestinal tract, and the 5-year survival rate for esophageal cancer patients is approximately 14% (12,13). Recently, although there are some studies on the relevance of adiponectin to malignancy, we have not found any information in the literature on the serum adiponectin levels in esophageal cancer. In this study, we therefore measured serum adiponectin levels in patients with esophageal cancer and investigated a possible relationship between serum levels of adiponectin and clinicopathological characteristics of the tumor such as stage, tumor location and histological type.

PATIENTS AND METHODS

STUDY POPULATION

The study was carried out in a total of 62 patients with esophageal cancer, admitted to the Medical Oncology
Department of Faculty of Medicine, Ataturk University. Subjects were excluded from the study if they were known to have any disease other than esophageal cancer. Thirty healthy volunteers were included in this study as the control group. Informed consent was obtained from participating subjects before the study, which was carried out according to the principles of the Declaration of Helsinki. All patients were newly diagnosed and none had received any form of anti-cancer therapy before collection of blood samples for biochemical analysis. The diagnosis of esophageal cancer was established by endoscopic examination of the esophagus and by biopsy confirmation. Tumors were classified into two types based on the histological characteristics: adenocarcinoma and squamous cell carcinoma of the esophagus. All staging of the patients with tumor were carried out according to the latest pathological tumour node metastasis criteria for carcinoma of the esophagus, established by the American Joint Committee on Cancer in 2002 (AJCC Cancer Staging Manual. 6th edn. New York: Springer-Verlag 2002).

Participants’ body weight and height were recorded at the time of first examination and body mass index (BMI) was calculated as kg/m². The clinical characteristics of the case and control participants, and the tumor characteristics of patients with esophageal cancer in the study population are summarized in Tables 1 and 2, respectively.

**Biochemical Assay**

Fasting venous blood samples were collected into non-additive vacutainer tubes, allowed to clot and then centrifuged at 3500 × g for 5 min. Serum aliquots were stored at −80°C until assayed and thawed immediately prior to the measurements of biochemical parameters. Circulating serum levels of adiponectin were determined with a commercially available enzyme-linked immunosorbent assay (ELISA) kit with sensitivity < 3 ng/ml and intra-assay variation was less than 10% (AviBion Human Adiponectin ELISA, Orgenium Lab., Finland). All assays were performed in duplicate according to the manufacturer’s instructions.

**Statistical Analysis**

Statistical analyses were performed with the SPSS 11.5 statistical package (SPSS Inc., Chicago, IL, USA). A P value less than 0.05 was considered statistically significant. Normality of the sample distribution of each continuous variable was tested with the Kolmogorov–Smirnov test. The independent-samples t test was employed to compare age and BMI values between cancer patients and healthy volunteers. Kruskal–Wallis and Mann–Whitney U non-parametric tests were used to compare levels of adiponectin among different cancer stages, locations and histological types. Correlations between variables were determined by Spearman’s rank test. Data are expressed as median (range) for age and mean ± standard deviation for the other parameters.

**RESULTS**

Patients and healthy control characteristics are given in Table 1. No significant differences were observed in age and BMI between patients and controls. Tumor characteristics (stage, histological type, location and esophageal obstruction) of patients with esophageal cancer are shown in Table 2. BMI values were not significantly different between the total patient group and healthy controls. However, the patients had relatively lower BMI values in stage IV than in other stages (data not shown).

Fifty percent of patients with esophageal cancer had stage III tumor but there was no stage I case in our patient population. Seventy-nine percent of the patients had squamous
cell carcinoma \( (n = 49) \) and 21\% had adenocarcinoma \( (n = 13) \). Most patients in the present study had partial (52\%) or complete (38\%) esophageal obstruction (Table 2).

Blood samples from patients with esophageal cancer and from the healthy controls were measured to determine serum adiponectin levels. The mean serum adiponectin level in the cancer group was significantly low compared with the adiponectin level in the healthy control group \( (76.1 \pm 18.7 \text{ ng/ml vs. } 98.9 \pm 24.8 \text{ ng/ml}, P < 0.001, \text{ Table 1}) \). As shown in Fig. 1, furthermore, adiponectin levels gradually decreased with increase in tumor stage \( (\text{stage II, } 86.2 \pm 13.9 \text{ ng/ml}; \text{stage III, } 76.8 \pm 15.8 \text{ ng/ml}; \text{stage IV, } 68.7 \pm 22.7 \text{ ng/ml}) \).

In our study, approximately 63\% of patients with esophageal cancer had the tumor in the lower third of the esophagus, and 35\% of all lower esophageal cancers accounted for adenocarcinoma (others squamous cell carcinoma, 65\%). When adiponectin levels in the cancer group were compared with tumor locations such as upper, middle and lower esophagus, statistically significant differences were not found \( (74.2 \pm 6.4 \text{ ng/ml, } 81.1 \pm 9.6 \text{ ng/ml and } 73.2 \pm 24.1 \text{ ng/ml}, \text{ respectively, } P > 0.05 \text{ for all, Fig. 2}) \).

The patients were divided into two groups according to histological type of tumor as squamous cell carcinoma and adenocarcinoma, and the serum adiponectin levels were compared between the two groups (Fig. 3). We detected a significant difference in serum adiponectin levels regarding histological types of esophageal cancer. The patients with adenocarcinoma of the esophagus had significantly lower values of serum adiponectin than patients with squamous cell carcinoma.

In the correlation analysis, there was no significant correlation between serum adiponectin levels and BMI in patients with esophageal cancer (data not shown).

**DISCUSSION**

In the present study, we measured serum adiponectin levels in patients with esophageal cancer and healthy controls, and evaluated a possible relationship between serum levels of adiponectin and clinicopathological characteristics of tumors. It has been reported by several authors that adiponectin has anti-inflammatory, anti-atherogenic and anti-diabetic properties \( (1,4–6) \). Also, although there are some current studies on the role of circulating adiponectin in patients with breast,
endometrial, renal, colon or gastric cancer (7–11), no report has appeared yet in the literature regarding serum adiponectin levels in esophageal cancer. Thus, to our knowledge, this is the first study reporting some alterations of serum adiponectin levels in patients with esophageal cancer.

Because there was no study evaluating the relationship between esophageal cancer and adiponectin, it was difficult to compare our findings. Therefore, we might well consider other studies investigating the clinical relevance of adiponectin in cancer for comparison. Goktas et al. (14) investigated plasma adiponectin levels in 30 patients with prostate cancer, 41 subjects with benign prostatic obstruction and 36 healthy controls. Their data showed that plasma adiponectin levels were significantly lower in the prostate cancer group than in other groups. Furthermore, a negative association between histological grade and stage of prostate cancer and plasma adiponectin levels was reported. In another study (15), in contrast to the previous results, it was reported that serum adiponectin concentration did not significantly differ between prostate cancer cases and healthy controls. Dal Maso et al. (7) analyzed 87 cases with endometrial cancer for plasma and serum adiponectin levels. They found an inverse association with endometrial cancer risk for plasma adiponectin levels, and similar results for serum adiponectin as well. Also, Mantzoros et al. (16) reported that there was a fairly robust inverse association of adiponectin with breast cancer risk among postmenopausal women but not among premenopausal women. The authors speculated that low levels of adiponectin may play a permissive role in stimulating the neoplastic growth of breast cells. Recently, Ishikawa et al. (8) determined plasma levels of adiponectin in 75 patients with gastric cancer and 52 healthy subjects, and have reported that a low plasma adiponectin level is associated with an increased risk of gastric cancer, especially in undifferentiated type cancer in the upper stomach.

As stated in the earlier paragraph, previous studies have shown that circulating adiponectin levels are generally decreased in some solid tumors (7,8,14,16). In the present study, we detected significant differences in mean serum adiponectin levels among study groups (lower in subjects with esophageal cancer than in those without). In addition, adiponectin levels gradually decreased with increase in tumor stage. Such a decrease in adiponectin levels was most significant in patients with stage IV esophageal cancer. In some previous studies, although an inverse association between the decreased levels of circulating adiponectin and cancer risk has been reported, the underlying mechanisms are still obscure. Brakenhielm et al. (17) have reported that adiponectin is a direct angiogenesis inhibitor (a negative regulator) that induces apoptosis in activated endothelial cells. It is well known that angiogenesis is critical for tumor growth and metastasis. Thus, a decreased adiponectin level may expedite the development of esophageal cancer.

In the present study, we did not investigate serum levels of growth factors but the decreased adiponectin levels in esophageal cancer could be associated with growth factors. Recent studies point out that the levels of increased insulin-like growth factor (IGF)-I and decreased IGF-binding protein (IGFBP)-III are related to raised frequency of development of various cancers including breast, prostate, lung, colon and esophageal cancer (18,19). IGF-I may inhibit apoptosis and increase production of the vascular endothelial growth factor (VEGF) (20). Adiponectin can also inhibit the activation of nuclear factor-κB, a transcription factor that up-regulates VEGF in breast cancer (16). Obesity-induced down-regulation of adiponectin expression increases breast cancer risk through a mitogenic effect of hyperinsulinemia and increased IGFs as well as by up-regulating VEGF (16). Higher levels of IGF-1 have been found in patients with esophageal cancer compared with healthy controls (19). Thus, it is reasonable to theorize that a possible association between adiponectin and IGF in progression of esophageal cancer exists but a further investigation is required to explain this relationship.

In our study, another important finding was that serum adiponectin levels were associated with histological types of esophageal cancer. The patients with esophageal adenocarcinoma had significantly lower adiponectin levels than those with squamous cell carcinoma. Ogunwobi et al. (21) examined the effects of leptin and adiponectin on proliferation of esophageal adenocarcinoma cell lines. Their data have shown that adiponectin inhibits leptin-induced proliferation in esophageal adenocarcinoma cells via adiponectin receptor-1 and activation of adenosine monophosphate-activated protein kinase and serine/threonine phosphatases. Adiponectin deficiency may contribute to the progression of esophageal adenocarcinoma and other obesity-associated cancers (21). Obesity is commonly accepted as one of the major risk factors for adenocarcinoma of the esophagus, probably via the increased rate of gastroesophageal reflux as a result of elevated intra-abdominal pressure (22–24). Konturek et al. (25) analyzed the expression of adiponectin receptor and the effect of adiponectin on apoptosis in Barrett’s adenocarcinoma cells in vitro. The authors reported that adiponectin has an inhibitory effect on Barrett’s carcinogenesis and the decrease in the level of adiponectin in obesity may explain the progression of Barrett’s carcinoma in obese individuals (25). Some authors reported that the blood adiponectin level inversely is related to BMI (26). On the contrary, in an experimental study, deletion of adiponectin in mice does not result in any difference in body weight (27). Similarly, overexpression of adiponectin in mice did not result in a significant difference of body weight (28). In our study, BMI values were not significantly different between patients with cancer and healthy controls. In addition, when compared with patients with squamous cell carcinoma, BMI did not differ from those with esophageal adenocarcinoma in the present study. Thus, it seems difficult to associate the observed difference in adiponectin levels according to histological type of esophageal cancer with BMI in the present work. Possibly, a further study is required to explain this relationship.
Ishikawa et al. (8) reported that adiponectin levels in patients with upper gastric cancer were lower than those in patients with cancers in the middle or lower part. This result is actually interesting, and may be a new research target. In our study, nevertheless, adiponectin levels in patients with esophageal cancer did not show any significant difference according to tumor location in esophageal tissue. This discrepancy between our study and that of Ishikawa et al. (8) might be due to the different cancer and tissue types analyzed.

**CONCLUSION**

We detected that serum adiponectin levels are significantly lower in patients with esophageal cancer, especially esophageal adenocarcinoma, than that in healthy controls. On the basis of these findings, we think that decreased circulating adiponectin levels may play a role in the progression and/or development of esophageal cancers. However, for the clinical use of serum adiponectin in terms of early diagnosis, detection of clinical relapse and follow-up treatment, further studies should be performed.

**Conflict of interest statement**

None declared.

**References**