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ORIGINAL PAPER

The association of serum adiponectin levels with histopathological variables in gastric cancer patients

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Abstract Adiponectin is a peptide hormone secreted from the adipose tissue, affecting the proliferation and insulin sensitivity in different cell types. The levels of adiponectin have been found to be decreased in hyperinsulinemia and insulin resistant states, such as obesity. The previous studies have suggested that plasma adiponectin levels are decreased in patients with endometrial and breast cancer. In our study, the relationship among serum adiponectin levels, demographic features and histopathological variables was evaluated in gastric cancer patients. Forty consecutive patients with gastric cancer who underwent gastrectomy with standard lymph node dissection were included and 43 healthy controls were included in this study. The serum levels of glucose, insulin, C-peptide, HbA1c and adiponectin were measured in both groups. We analyzed the correlation among these parameters and patients' demographic features, such as age, gender, body mass index (BMI) and histopathological variables such as tumor localization, stage, nodal status, histological grade, vascular and lymphatic invasion. The mean age was 60.05 + 9.72 in patients, while it was 38.6 + 12.73 in controls. The mean serum adiponectin levels were 12.62 + 7.9 and 10.07 + 6.72 ng/ml, respectively, in groups. There was no different in terms of adiponectin, C-peptide, HOMA-R level in both groups. On the other hand, BMI, glucose and insulin levels were significantly different in gastric cancer patients in comparison with the controls. There was no correlation among the levels of adiponectin, BMI, insulin and c-peptide levels in patient group ($P > 0.05$). The adiponectin levels of woman were significantly lower than male patients ($P = 0.002$). No relations were detected among tumor stage, tumor localization, nodal status, lymphatic and vascular invasion, and the levels of serum adiponectin ($P > 0.05$). Interestingly, a positive correlation was found between tumor grade and plasma adiponectin levels ($r = 0.372$; $P = 0.018$). Our results suggest that plasma adiponectin levels were similar in both patients with gastric cancer and the controls. In addition, no correlation was found between adiponectin levels and demographic features and histopathological variables of patients. But, in undifferentiated tumors, plasma adiponectin level was significantly higher than well-differentiated grade tumors.

Keywords Serum adiponectin · Gastric cancer · Histopathological variables

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Introduction

Obesity is a risk factor for the development of cardiovascular disorders and diabetes, which are closely linked to

angiogenesis. In addition, it has recently been shown to be associated with increased risk for malignancies at multiple specific sites [1, 2]. In gastric cancer, obesity is documented to be associated especially with the development of adenocarcinoma in the cardiac region [3, 4.] This association is thought to be explained partly by the increased rate of gastroesophageal reflux disease as a result of increased intra-abdominal pressure [5–7]. Nevertheless, the reflux theory cannot explain every aspect of the manifestation of gastric cancer, and the epidemiologic study raises a hypothesis that adipose tissue might be functionally involved in the development of gastric cancer.

Adipocytokines, such as adiponectin and leptin, are cytokines secreted primarily by visceral adipose tissue [8, 9]. Adiponectin is a 247-amino acid adipocytokine with an increasingly important role in energy homeostasis and insulin sensitivity. It was isolated during adipocyte differentiation of 3T3-L1 and 3T3-F442A fibroblasts and from large-scale sequencing of the human adipose cDNA library [10]. The negative correlation between plasma adiponectin levels and obesity [11], adiposity, and waist to hip ratio [12], diabetic dyslipidemia [13], cardiovascular disease [14] and insulin resistance [12] has been reported in human cross-sectional studies. On the other hand, circulating adiponectin levels seem to associate more with hyperinsulinemia and insulin resistance than obesity or body fat [12]. The case–control studies showed that low plasma adiponectin was an independent risk factor for future development of type 2 diabetes [15], but not for obesity [16]. Since the circulating adiponectin levels are reduced in obesity, this adipokine may have an important protective role against carcinogenesis.

Previous studies have indicated that serum adiponectin levels are decreased in patients with breast or endometrial cancer [17–19]. Similarly, they showed that plasma adiponectin level was significantly lower in gastric cancer patients than in healthy controls [5, 20]. Furthermore, it reported that plasma adiponectin level is negatively correlated with tumor stage [5].

The aim of the present study was to investigate the nature of the relationship between serum adiponectin levels and insulin-resistance parameters, such as, glucose, insulin, BMI, C-peptid, HOMA in gastric cancer patients. In addition, the association of plasma adiponectin level with histopathological parameters was also evaluated.

Material and method

Totally 40 patients with gastric cancer who underwent a curative gastrectomy by standard lymph node dissection at Department of Medical Oncology, Dr. Lutfi Kirdar Kartal Education and Research Hospital were enrolled in this study. Clinical informations about age, gender, resection type, tumor location, histopathology, tumor stage, tumor size, histological grade, lymph node involvement, the depth of tumor invasion, lymphatic and vascular invasion were obtained from patients charts. Tumor localization was classified as fundus, corpus and antrum.

The patients who had no distant metastasis and diabetes mellitus were included in the study, thereafter, fasting blood samples were collected to determine the values of adiponectin, C-peptide, insulin, glucose, hemoglobin A1c (HbA1c).

Insulin resistance was calculated using the method of "homeostasis model assessment (HOMA)". In addition, blood samples were also collected from control group which include 43 subjects who did not show gastric cancer during physical examination and upper gastrointestinal examination during 2007. Body mass index (BMI) was calculated according to Quetelet's formula as the ratio of body weight to body height squared (kg/m^2). Serum dissociation was rapidly performed and it was stored at −80°C until the use. Plasma adiponectin levels were measured using 'Human Adiponectin' (ARCP 30) kit produced by Linco Research (USA). This method is a sandwich ELISA in which double monoclonal adiponectin antibody is used (Cat.EZHADP-6 K).

The patients were categorized into three groups according to the degree of differentiation. Grade 1, well-differentiated tumors; grade 2, moderately differentiated tumors; grade 3, poorly or undifferentiated tumors. Informed written consents were obtained from each subject included in the study.

Statistical methods

Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA) software. Descriptives of the parameters are quoted as mean ± SD and 95% confidence intervals (CI). Mann–Whitney U test was used for the comparison of non-normally distributed variables. To compare categorical variables, chi-square test was also applied. *P*-values less than or equal to 0.05 were considered to be statistically significant.

Results

Forty patients consisting of 30 male and 10 female with gastric cancer who underwent a gastrectomy by regional lymph node dissection for curative intent were included. After diagnosis, the mean age was 60.05 ± 9.72 years (range: 36–76 years), the mean BMI was 23.77 ± 4.60 kg/m^2, the mean adiponectin level was 12.62 ± 7.90 ng/ml, the mean glucose level was 94.05 ± 12.90 mg/dl, the

mean insulin level was 10.40 ± 12.54 (mg/dl), the mean C-peptide level was 3.35 ± 2.2 mg/dl and HOMA was 2.52 ± 3.45. There was no correlation between plasma adiponectin levels and BMI, insulin, c-peptide levels in patients group ($P > 0.05$).

Plasma adiponectin levels in woman were significantly lower than those in male patients ($P = 0.002$). No relations were found between tumor stage, tumor localization, lymph node status, lymphatic and vascular invasion, and serum adiponectin levels ($P > 0.05$). Interestingly, the correlation between tumor grade and adiponectin levels was found ($r = 0.372$; $P = 0.018$, Fig. 1).

Control group consisted of a total of 43 patients. The mean age was 38.60 ± 12.73 years and the mean BMI was 27.48 ± 4.47 kg/m^2 in the control group. Furthermore, the mean adiponectin level was 10.07 ± 6.72 ng/ml, the mean glucose level was 88.27 ± 11.35 mg/dl, the mean insulin level was 10.17 ± 5.19 (mg/dl), the mean C-peptide level was 2.58 ± 0.68 mg/dl and HOMA-R was 2.23 ± 1.46. Demographics and investigational data of patient and control groups are summarized in Table 1.

Serum adiponectin, C-peptide levels and HOMA were not significantly different between patient and control groups ($P = 0.145$, 0.343, and 0.081, respectively). But BMI, glucose and insulin levels were significantly different between in two groups ($P = <0.001$, $P = 0.034$, 0.049, respectively). Plasma adiponectin levels were not different according to tumor localization (20.2 in fundus, 19.3 in corpus and 20.9 in antrum, $P > 0.05$). In the patient group, adiponectin levels proportionally increased with an increase in tumor grade (Figure 1).

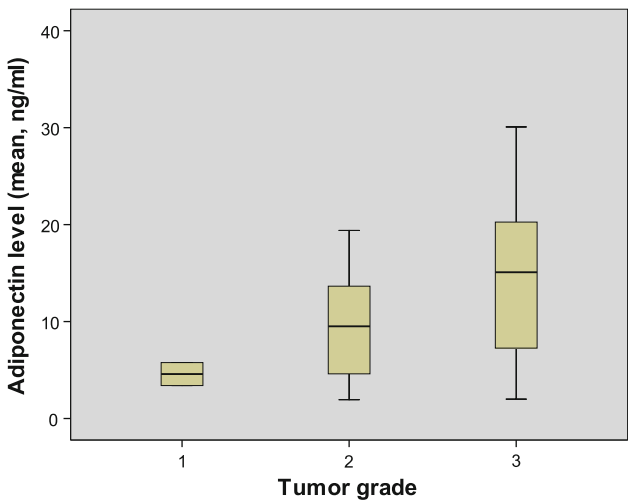

Fig. 1 Correlation between tumor grade and plasma adiponectin levels in patients with gastric cancer

Discussion

Two case–control studies have been reported regarding serum adiponectin level in gastric cancer patients until now [5, 20]. In a study including 75 gastric cancer patients and 52 healthy controls carried out by Ishikawa et al., plasma adiponectin level was significantly lower in patients than that in healthy controls [5]. In addition, they showed that a significant modest inverse relation was found between plasma adiponectin levels and gastric cancer, although BMI was not significantly different. The authors concluded that a low plasma adiponectin level was associated with an increased risk of gastric cancer.

Generally, gastric cancer patients tend to be cachexic with low BMI levels, since most of them have gastrointestinal symptoms such as epigastralgia, nausea and anorexia. Consequently, it is difficult to match BMI level between gastric cancer patients and controls, indicating the difficulty in elucidating the pathophysiological significance of adipocytokines in gastric cancer carcinogenesis or tumor progression independently from cachexia or BMI level [5]. In our study, we did not detected significant different in terms of plasma adiponectin, C-peptide and HOMA-R levels in both patients with gastric cancer and control groups. These results were not compatible with literature. The cause of this difference may be related to small sample size of our study.

Second trial recently reported by Nakajima et al. In their trial, the levels of BMI, adiponectin, leptin, resistin, visfatin and C-peptide in blood samples at the diagnosis were measured in 156 gastric cancer patients and 156 age- and sex-matched controls [20]. They indicated that plasma adiponectin, C-peptide and BMI levels were significantly lower, and resistin and visfatin levels were significantly higher in the patients on multivariate analysis. However, the inverse correlation between BMI and adiponectin was comparatively strong in the controls, but was weak in the patients. Moreover, the authors have compared 38 patients with stage I gastric cancer with the controls according to plasma adiponectin levels in subgroup analysis and they showed that serum adiponectin level tended to decrease in the patients, and BMI level was not different between two groups [20].

Nutritional status in patients with cancer might also affect the serum adiponectin level. Nevertheless, Ishikawa et al. indicated that none of preoperative albumin, total protein, total cholesterol, triglyceride and cholinesterase showed a significant association with adiponectin level in their series. This indicates that the difference in plasma adiponectin level was not attributable to the nutritional status.

First trial performed by Ishikawa et al. indicated that the stage was inversely correlated with the plasma adiponectin

Table 1 Demographics and investigational data of patient and control groups

Factor	Patients ($n = 40$) Mean ± SD	Control group ($n = 43$) Mean ± SD	P value
Age (years)	60.05 ± 9.72	38.60 ± 12.73	<0.001
BMI (kg/m^2)	23.77 ± 4.60	27.48 ± 4.47	<0.001
Adiponectin (ng/ml)	12.62 ± 7.90	10.07 ± 6.72	0.145
Glucose (mg/dl)	94.05 ± 12.90	88.27 ± 11.35	0.034
Insulin (mg/dl)	10.40 ± 12.54	10.17 ± 5.19	0.049
C-peptide	3.35 ± 2,29	2.58 ± 0.68	0.343
HOMA	2.52 ± 3.45	2.23 ± 1.46	0.081

HOMA homeostasis model assessment

level in undifferentiated gastric cancer [5]. However, they were not observed this tendency in patients with differentiated gastric cancer. This was a clear contrast between the two groups and thus may reflect a biological difference between differentiated and undifferentiated gastric cancer. First, the authors suggested the possible role of adiponectin in tumor progression [5], although such a relationship between plasma adiponectin level and tumor stage has never been described in previous studies [17–19, 21].

In our study, a positive correlation was found between tumor grade and plasma adiponectin levels as similar to the study of Ishakawa et al. [5] They indicated that the stage was inversely related to the plasma adiponectin level in undifferentiated gastric cancer, but this tendency was not detected in patients with differentiated gastric cancer. This finding shows the possibility that low plasma adiponectin level may prevent invasion or metastasis. In addition, a decrease in adipokine creates favorable factor for tumor spread in gastric cancer.

In case–control studies, the significant decrease in adiponectin levels has been previously documented in patients with breast, endometrial, prostate, colon cancers and myelodysplastic syndrome (MDS) in addition to gastric cancer [5, 22, 23]. Furthermore, the expressions of the adiponectin receptor in cancer cells have been identified in prostate, hepatocellular and gastric cancer cells in vitro, and the direct function of adiponectin in cancer cells has been demonstrated [24].

In conclusion, we found that plasma adiponectin, C-peptide and HOMA-R levels in patients with gastric cancer was similar to those in the controls, but BMI, glucose and insulin levels were significantly different in both groups. In addition, the adiponectin levels in woman were significantly lower than those in male patients. In undifferentiated tumors, plasma adiponectin level was significantly high. Raising the possibility that adiponectin has a potential role in the progression of gastric cancer, especially undifferentiated tumors.

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