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Serum Adiponectin Relates to Shortened Overall Survival in Men with Squamous Cell Esophageal Cancer Treated with Preoperative Concurrent Chemoradiotherapy: A Pilot Study

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Background: The convergence of nutritional, genetic, and inflammatory factors plays a significant role in the pathophysiology of squamous cell esophageal cancer (SCEC). The parameters of inflammation, indices of nutritional status, and adipocyte-derived hormones such as leptin, adiponectin, and resistin have been shown to be prognostic factors in some gastrointestinal and pancreatic cancers.

Material/Methods: Forty-two patients with SCEC were subjected to a multimodal regimen of concurrent neoadjuvant chemoradiotherapy (CRT) followed by surgery. We retrospectively analyzed the impact of pretreatment values of serum leptin, adiponectin, resistin, soluble leptin receptor, C-reactive protein, TNF alpha, leukocytes, and indices of nutritional status (BMI, plasma total protein, albumin, cholesterol, and triacylglycerols) on overall survival (OS).

Results: Univariate analysis revealed significant a negative correlation between OS and serum adiponectin (p=0.027), and a positive relationship was found between serum albumin (p=0.002), cholesterol (p=0.049) level, and OS. In multivariate analysis, only the trend (p=0.086) for negative serum adiponectin association with the OS was observed.

Conclusions: In men with SCEC treated by neoadjuvant concurrent CRT and esophagectomy, high pretreatment level of serum adiponectin was associated with shorter OS while the serum albumin and cholesterol were associated with longer OS.

MeSH Keywords: Adiponectin • Chemoradiotherapy • Esophageal Neoplasms • Serum Albumin • Survival

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Background

Incidence of esophageal cancer has been rising dramatically in the last decades. Worldwide, esophageal cancer is the eighth most common malignancy and the sixth most common cause of cancer-related death; long-term survival is only 10% [1]. In the Czech Republic, yearly incidence rate was about 600 cases of esophageal cancer [2]. Nowadays, combined concurrent chemoradiotherapy followed by surgery is the most frequently used treatment modality for operable esophageal cancer [3]. Contemporary clinical research is concerned with looking for the prognostic markers facilitating individual treatment choice [4,5]. Smoking, alcohol consumption, and nutritional imbalance are risk factors for squamous cell esophageal cancer (SCEC), and Barrett's esophagus, gastroesophageal reflux, and obesity increase the risk of esophageal adenocarcinoma [6].

The chronic inflammation, caused by both infective and noninfective irritants, in concert with genetic factors, plays a significant role in the pathophysiology of gastrointestinal and pancreatic cancers, including SCEC [7–9]. For instance, in patients who have undergone potentially curative resection for colorectal cancer, preoperative concentration of C-reactive protein (CRP) was independently associated with overall and cancer-specific survival [10]. Serum albumin, which is considered a significant parameter of nutritional status in patients with cancer, can serve as another prognostic factor, being negatively influenced by both malnutrition and inflammation [11]. Dysregulated adipocyte-derived hormones such as leptin, adiponectin, and resistin also take part in the pathophysiology of esophageal cancer [9,12,13].

Leptin plays an important role in the regulation of appetite and metabolism and influences immune and neuroendocrine functions, hematopoesis, angiogenesis, and bone remodeling. Leptin exerts its effects through binding and activating specific leptin receptors [14]. Ob-Re, or soluble leptin receptor (SLR), circulates in plasma and has major leptin-binding activity [15]. Increased concentrations of serum leptin were described in several tumors, such as breast cancer, gastric, endometrial, prostatic, or esophageal cancer [16], and unchanged or decreased levels of leptin in cancers were described as well [17,18]. There are only a few studies examining the relations of SLR to cancers, with inconsistent results [19,20].

Adiponectin is a 244 amino acid protein that is synthesized by adipose tissue. Adiponectin inhibits energy expenditure, promotes food intake centrally, and stimulates free fatty acids utilization in peripheral tissues [21,22]. In different cancers, such as breast cancer, endometrial, or prostate cancer, lowered levels of serum adiponectin are usually found [23].

Resistin belongs to a family of cystine-rich peptides called resistin-like molecules [24]. In humans, resistin is secreted mainly in mononuclear cells, which could indicate its potential relation to the inflammatory process [21,25]. Increased plasma levels of resistin were described in breast cancer [26], endometrial cancer [27], in non-small cell lung cancer [28] and in colorectal cancer [29]. On the other hand, decreased resistin levels were found in multiple myeloma [30]. Increased levels of resistin were found in esophageal squamous cancer [31], correlating with the progression of the disease.

The aim of this study was to investigate retrospectively whether pretreatment serum concentrations of leptin, soluble leptin receptors, adiponectin, and resistin, together with inflammation indicators (TNF-alpha, CRP, white blood cell count), and parameters of nutritional status (albumin, hemoglobin, and plasma lipids), influence overall survival (OS) in men with SCEC after esophagectomy with concurrent chemoradiotherapy (CRT).

Material and Methods

Patients

After providing signed informed consent, 42 patients with SCEC were subjected to a multimodal regimen of concurrent neoadjuvant CRT followed by surgery. Patients had histologically-proven squamous carcinoma of the esophagus and resectable tumor in stage II or III of disease defined by the TNM system and the American Joint Committee on Cancer Classification [32]. The treatment protocol was approved by the institution and by the Ethics Committee of the General Faculty Hospital and 1st Faculty of Medicine, Charles University, Prague. All experiments were performed in compliance with relevant national laws. Protocol of CRT based on cisplatin plus fluorouracil and concurrent radiotherapy 45 Gy/25 fractions/5 weeks followed by esophagectomy has been published in detail elsewhere [33]. After surgery or definitive CRT, patients were followed up without further adjuvant therapy.

Laboratory analyses

Blood samples were obtained after 12 h of fasting. Leptin serum levels were measured, as well as those of soluble leptin receptor (SLR), adiponectin, and resistin, using commercial ELISA kits of BioVendor, Brno, Czech Republic (Leptin: RD191001100 HUMAN LEPTIN ELISA, CLINICAL RANGE, SANDWICH IMMUNOASSAY; soluble leptin receptor (SLR): RD194002100 HUMAN LEPTIN RECEPTOR ELISA, SANDWICH IMMUNOASSAY; insulin-like growth factor 1 (IGF 1): RMEE20 Human IGF-1 ELISA, SANDWICH IMMUNOASSAY; adiponectin: RD195023100 HUMAN ADIPONECTIN ELISA, COMPETITIVE IMMUNOASSAY; and resistin: RD191016100 HUMAN RESISTIN ELISA, SANDWICH IMMUNOASSAY). The TNF-α was measured with the commercial kit of R&D systems, Inc., Minneapolis, MN, USA (TNF-α: DTA00C

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Table 1. Baseline clinical characteristics and impact of the variables on overall survival.

Variable	Number	Percent	p-value*
WHO performance status			
0	4	9.5	
1	36	85.7	
2	2	4.8	0.668
Risk factors			
Smoking	39	92.9	0.146
Alcohol daily	34	81.0	0.475
TNM stage			
T2	2	4.8	
T3	34	81.0	
T4	6	14.3	0.326
N0 M0	18	42.9	
N1 and/or M1a	24	57.1	0.366
	Mean (range)		p-value**
Age (years)	58.0 (44–75)		0.772
Body weight (kg)	72.8 (52–105)		0.232
Body mass index (kg·m^{-2})	23.5 (16.2–31.7)		0.154

* Long-rank test for comparison of two or more survival curves; ** Cox Proportional Hazards Regression Model.

Human TNF-alpha Quantikine ELISA, SANDWICH IMMUNOASSAY). Routine analyses (cholesterol, triacylglycerols, albumin, total protein, C-reactive protein, hemoglobin, leukocytes, and lymphocytes) were measured by standard methods.

Statistical methods

The impact of several clinical prognostic variables on overall survival was assessed using univariate analysis (log-rank tests for categorical variables and univariate Cox Proportional Hazards Regression Models for continuous variables). Besides clinical factors such as body weight, body mass index, sex, age, alcohol abuse, smoking status, T and N stage and performance status, we investigated the following laboratory indicators: total serum protein and albumin level, serum concentrations of cholesterol, triacylglycerols, adiponectin, leptin, SLR, resistin, and the concentrations of serum TNF-α and CRP before CRT. Multivariate analysis for the risk factors was performed using the multivariate Cox Proportional Hazard Regression model. Variables with a value $p<0.10$ on univariate analysis were incorporated into the multivariate model. For descriptive purposes, basic statistics (mean, median, standard deviation) were calculated for all continuous data. Statistical significance was reported at levels of $p<0.05$ and trends were identified at $p<0.10$. All statistical analyses were performed in the program Statistica, version 7.0. (StatSoft, Inc., Tulsa, Oklahoma, USA, 2004, version 7, *www.statsoft.com*).

Results

Forty-two men were treated according to the aforementioned protocol during January 2001 to August 2005. Basic clinical characteristics of the studied group are presented in Table 1.

Mean age of the patients was 58.0 years; average body weight and body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, of patients before start of treatment were 72.8±13.2 kg (mean ± standard deviation) and 23.5±4.2 kg·m^{-2}, respectively. After a median follow-up of 52 months (range 27–80), the median survival was 15 months, and 1- and 3-year survival were 55% and 21%, respectively. Results of laboratory analysis of pretreatment blood sample are summarized in Table 2.

Univariate and multivariate analysis of survival data

The impact of prognostic variables on OS was assessed using univariate analysis. Univariate analysis of clinical variables (Table 1) did not reveal any significant prognostic factor.

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Table 2. Baseline laboratory findings of the studied group.

Variable (unit)	Normal range (men)	Mean	SD	Range in the study group
Leukocytes (10^9/l)	4.1–10.2	8.5	2.3	3.28–14.2
Hemoglobin (g/l)	135–174	152.9	71.7	113–162
Total protein (g/l)	65–85	73.1	5.8	54–86.9
Albumin (g/l)	35–53	40.4	4.6	22–47.3
CRP (mg/l)	0–7	13.1	16.2	1.9–61.2
Cholesterol (mmol/l)	2.9–5.2	4.94	1.01	3.0–7.39
Triacylglycerols (mmol/l)	0.45–1.7	1.36	0.68	0.54–4.59
TNF-alpha (µg/l)	NS	1.21	0.96	0.07–3.78
Leptin (µg/l)	NS	4.47	5.78	0.1–25.1
Soluble leptin receptor (U/ml)	NS	34.02	29.04	12.2–203.9
Adiponectin (mg/l)	NS	31.32	21.56	6.5–106.2
Resistin (µg/l)	NS	7.67	4.01	2.3–19.9

SD – standard deviation; CRP – C-reactive protein; TNF-alpha – tumor necrosis factor alpha; NS – not specified.

Table 3. Prognostic influence of laboratory variables on survival – univariate analysis.

Variable	Hazard ratio	95% CI	p-value*
Leukocytes	1.165	(0.998; 1.359)	0.053
Hemoglobin	0.99	(0.976; 1.004)	0.168
Total protein	0.99	(0.923; 1.063)	0.788
Albumin	0.902	(0.845; 0.963)	**0.002**
CRP	1.022	(0.999; 1.045)	0.060
TNF-alpha	1.365	(0.956; 1.95)	0.087
Cholesterol	0.668	(0.447; 0.999)	**0.049**
Triacylglycerols	0.845	(0.493; 1.44)	0.539
Leptin	0.96	(0.898; 1.027)	0.233
Soluble leptin receptor	1.002	(0.992; 1.012)	0.743
Adiponectin	1.018	(1.002; 1.033)	**0.027**
Resistin	1.035	(0.944; 1.135)	0.461

* Cox Proportional Hazards Regression Model.

The results of univariate analysis of relations between laboratory analytes and OS are summarized in Table 3. Significant impact on OS was shown for the following variables: serum adiponectin (HR 1.018, p=0.027), serum cholesterol (HR 0.668, p=0.049), and serum albumin (HR 0.902, p=0.002); moreover, trend was found for leukocytes (HR 1.165, p=0.053), and CRP (HR 1.022, p=0.060).

Multiple regression (Cox) analysis (Table 4) was performed to identify factors that were independently associated with overall survival time. Backward selection analysis identified no significant prognostic factor. Trend to significance was only noticed in the case of adiponectin (HR 1.018, p=0.086). The influence of pretreatment serum adiponectin on OS is depicted in Figure 1.

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Table 4. Results of multivariate analysis.

Variable	Hazard ratio	95% CI	p-value*
Leucocytes	1.039	(0.862; 1.251)	0.690
Albumin	0.949	(0.797; 1.13)	0.557
CRP	1.026	(0.988; 1.065)	0.184
Cholesterol	0.807	(0.446; 1.462)	0.480
TNF-alpha	1.361	(0.819; 2.261)	0.235
Adiponectin	1.018	(0.997; 1.039)	0.086

* Cox Proportional Hazards Regression Model.

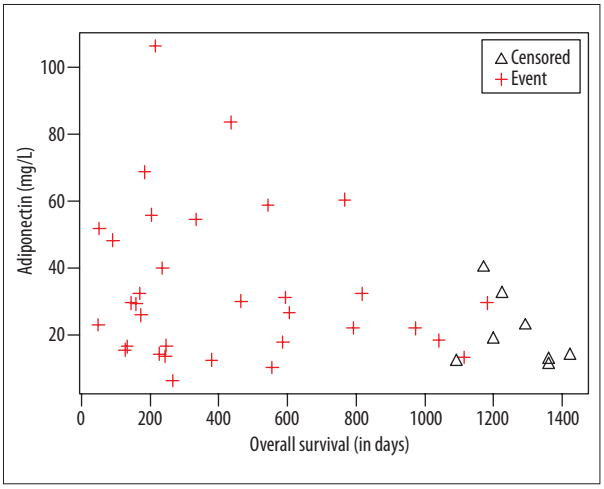

Figure 1. Influence of pretreatment serum adiponectin on overall survival.

Discussion

In this study we analyzed the impact of pretreatment serum adipokines (leptin, adiponectin, resistin, and soluble leptin receptor), indicators of both inflammation (CRP, TNF-alpha, leukocytes) and nutritional status (pretreatment BMI, plasma total protein, albumin and lipids) on OS of men with esophageal cancer, treated with esophagectomy and concurrent CRT. Univariate analysis revealed a significant negative correlation between OS and serum concentrations of adiponectin, whereas a positive relationship was found between serum albumin and cholesterol levels and OS. Borderline negative relationship between the white blood cell count and OS was also observed. In multivariate analysis, only the trend for the serum adiponectin association with the OS was observed. This may suggest that variables revealed to be significantly associated with the OS in the univariate analysis probably operate interdependently, being indicators of nutritional status and the inflammatory microenvironment. Good nutritional status is connected with better results of treatment of the patients with EC treated by esophagectomy and concomitant CRT [34,35]. Both serum albumin and cholesterol can serve as laboratory markers of nutritional adequacy [36]. Low serum albumin and weight loss were found to be independent indicators of poor prognosis in patients with carcinoma of the esophagus treated with CRT [37]. In a recent meta-analysis of 59 studies, pretreatment serum albumin was reported to be a significant prognostic factor of overall survival [11]. Similarly, preoperative total serum cholesterol may be an important prognostic factor for overall survival of the patients with cancer, as was observed in patients after lung cancer resection [38]. Markers of inflammation such as an elevated white blood cell count were found to be independently associated with total and non-small cell lung cancer mortality [39], or with an increase in both the mortality and incidence rate of colon cancer [40]. Circulating concentrations of serum adiponectin levels are usually negatively associated with the risk of several malignancies, such as prostate [41], colorectal [42], or gastric cancer [43]. Mechanisms by which adiponectin could function against cancer initiation and progression have been reviewed elsewhere [44]. Until now, only 2 studies have investigated serum adiponectin level in esophageal cancer. One study found that cancer patients have significantly lower concentrations of adiponectin in comparison with controls, and adiponectin level decreased with increasing tumor stage [45]. The second study found no significant differences in adiponectin levels between controls, esophageal cancer, basal cell dysplasia, dysplasia group, and esophageal cancer group [46]. On the other hand, elevated serum adiponectin levels were independently associated with childhood non-Hodgkin lymphoma (NHL) [47]. In pancreatic cancer, increased levels of adiponectin were also found [48]. In the other study, unchanged adiponectin, but increased adiponectin-to-leptin ratio, were described in pancreatic cancer patients [18]. Recently, increased adiponectin-to-leptin ratio was identified as a suitable marker of endometrial cancer in postmenopausal women [49].

To our knowledge, our study is the first to have found that higher pretreatment serum adiponectin concentration are

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associated with significantly shorter OS in patients with SCEC, treated with esophagectomy and concurrent CRT.

Several mechanisms may potentially be involved in this association. Increased adiponectin could compensate for insulin resistance, or for the adiponectin resistance [48,50]. Increased adiponectin could compensate for the inflammatory state, as was found in chronic inflammatory diseases such as type 1 diabetes mellitus, or rheumatoid arthritis [51,52]. Disease-induced weight loss could be another cause of an elevated adiponectin level [48]. Decreased concentration of adiponectin in obese patients and its increase after weight loss has been repeatedly observed [53], but the situation in cancer patients is more complicated. There was no correlation between adiponectin levels and cachexia in breast and colon cancer patients [50], nor in colorectal and lung cancer patients [54]. Moreover, dysregulated adiponectin was found in pancreatic cancer [18]. In this study, we observed no significant correlation between weight loss in the 3 months before examination and adiponectin (data not shown).

Conclusions

Using univariate analysis, we found that high pretreatment level of serum adiponectin was associated with shorter OS, and that the serum albumin and cholesterol levels were associated with longer OS of patients with SCEC, treated with esophagectomy with concurrent CRT. The worse prognosis of those patients could be connected with the inflammatory process and dysregulation of adiponectin, as well as nutritional status. Relatively small sample size was the limitation of the study. Therefore, further research on adiponectin functioning in the inflammatory state and esophageal cancer prognosis is needed.

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