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The evaluation of plasma arginine, arginase, and nitric oxide levels in patients with esophageal cancer

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Aim: Many studies have been conducted to investigate plasma arginine, arginase, and nitric oxide (NO) levels in patients with different types of cancer, and it has been suggested that these might be important factors for patients with cancer. In the present study, plasma arginine, arginase, and nitric oxide levels were evaluated in patients with esophageal cancer.

Materials and methods: A total of 100 patients (51 females and 49 males) diagnosed with esophageal cancer but not yet operated on were included in the study. The mean age of the study population was 62.03 ± 12.4 years. Patients treated with radiotherapy or chemotherapy were excluded. The control group included 80 subjects (38 females and 42 males) with a mean age of 57 ± 12.4 years. Plasma arginine, NO levels, and arginase activity were measured. High-performance liquid chromatography, Griess reactions, and modified Geyer and Dabich methods were used to detect the arginine levels, NO levels, and arginase activity.

Results: In patients with esophageal cancer, plasma arginine concentrations were significantly lower and NO levels and arginase activity were significantly higher than in the control groups ($P < 0.0001$, $P < 0.0001$, and $P = 0.005$, respectively). The sensitivity of arginase and NO were estimated at 87% and 89%, with respective specificities of 65% and 66%. Between the patients with and without distant organ metastasis, there were no significant differences in arginine/NO levels and arginase activity ($P > 0.05$). Similarly, there were no significant differences in these parameters between the patients with squamous cell carcinoma and adenocarcinoma ($P > 0.05$).

Conclusion: The results demonstrate that plasma NO levels and arginase activity may be used as markers for the diagnosis of esophageal cancer. However, larger and more comprehensive studies are needed.

Key words: Esophageal cancer, arginase, arginine, nitric oxide

Özofagus kanserli olgularda plazma arginin, arginaz ve nitrik oksit seviyelerinin değerlendirilmesi

Amaç: Çeşitli kanserlerde plazma arginin, arginaz ve nitrik oksit (NO) ile ilgili birçok çalışma yapılmış ve bu parametrelerin kanser hastaları için belirleyici faktörler olabileceği ileri sürülmüştür. Bu çalışmada özofagus kanserli hastalarda plazma arjinin, arjinaz ve nitrik oksit seviyeleri değerlendirildi.

Yöntem ve gereç: Çalışmaya özofagus kanseri tanısı konup henüz opere edilmemiş 51'i kadın ve 49'u erkek olmak üzere 100 hasta dahil edildi. Olguların yaş ortalamaları 62,03 ± 12,4 idi. Radyoterapi veya kemoterapi alan hastalar çalışmaya dahil edilmedi. Yaş ortalamaları 57 ± 12,4 olan 38 kadın ve 42 erkek olmak üzere 80 bireyden oluşan kontrol grubu oluşturuldu. Olguların plazma arginin ve NO düzeyi ile arginaz aktivitesi ölçüldü. Arginin düzeyi yüksek performanslı likit kromatografi yöntemi, nitrik oksit düzeyi Griess reaksiyonuyla, arginaz aktivitesi ise modifiye Geyer ve Dabich metoduyla ölçüldü.

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Bulgular: Plazma arginin konsantrasyonu özofagus kanserli hastalarda kontrol grubuna oranla belirgin derecede düşük, nitrik oksit düzeyi ve arginaz aktivitesi ise kontrol grubuna oranla önemli derecede yüksek bulundu (sırasıyla P < 0,0001, P < 0,0001 ve P = 0,005). Arginaz ve nitrik oksitin sensitivitesi % 87 ve % 89, spesifitesi ise % 65 ve % 66 olarak hesaplandı. Arginin, nitrik oksit düzeyleri ve arginaz aktivitesi, uzak organ metastazı olan hastalar ile metastaz olmayan hastalarla kıyaslandığında istatistiksel olarak anlamlı bir fark bulunmadı (P > 0,05). Benzer şekilde bu parametreler yassı epitel hücreli karsinom ve adenokarsinomalı hastalar ile kıyaslandığında da istatiksel olarak anlamlı bir fark saptanmadı (P > 0,05).

Sonuç: Elde ettiğimiz sonuçlar özofagus kanserli hastaların tanısında plazma NO düzeyi ile arginaz aktivitesinin bir tümör belirteci olarak kullanılabileceğini göstermektedir. Ancak bununla ilgili daha kapsamlı ve ileri düzeyde çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Özofagus kanseri, arginaz, arginin, nitrik oksit

Introduction

Nitric oxide is one of the free oxygen radicals produced by nitric oxide synthase (NOS) activity from arginine and it has double-sided effects. NO is necessary for many physiological functions and it contributes to antioxidant defense. In addition, it has a radical effect in the event of overproduction and causes more radical compounds such as peroxynitrite (1).

Increased arginase activity may limit NOS activity and lead to a weakening of the inhibitor effect on xanthine oxidase activity. In this case, it results in more superoxide radical production and tissue damage (2).

Since arginine is the nitrogen donor in NO synthesis, recently there has been an increased interest in this amino acid. The biochemistry of arginine, which is the precursor of NO and polyamines, stimulating the secretion of endogenous growth hormone with positive effects on wound healing and immunological aspects, is complex and involves many of the main metabolic pathways and organ systems (3-5).

The present study aimed to evaluate plasma arginine, arginase, and NO levels in patients with esophageal cancer; to evaluate the differences between patients with squamous cell carcinoma and adenocarcinoma in terms of plasma arginine, arginase, and NO levels; and to evaluate the differences between patients with and without distant organ metastasis in terms of plasma arginine, arginase, and NO levels.

Materials and methods

Patient selection

In the present study, 100 patients (51 females and 49 males) diagnosed with esophageal cancer but not yet operated on at the Ataturk University Medical Faculty Research Hospital's Thorax Surgery Department in 2008 and 2009 were included. Patients treated with radiotherapy or chemotherapy were excluded. Patients with systemic chronic diseases such as diabetes or hypertension were not included. Patients using any drugs were excluded.

The mean age of the patients was 62.03 ± 12.4 years. The control group included 80 healthy subjects with 38 females and 42 males. The mean age of the control group was 57 ± 12.4 years.

Collection of blood samples

Venous blood samples were taken from the patient and control groups into tubes containing ethylenediaminetetraacetic acid (EDTA). The tubes were placed in a cooled centrifuge at 2000 rpm for 10 min at 10-18 °C, and then the obtained plasma was stored in Eppendorf tubes at –80 °C until analysis. Thawing was permitted only once and the samples were checked for significant hemolysis or lipemia. The frozen samples were thawed at room temperature.

Arginase measurement

Plasma arginase activity was studied using the Geyer and Dabich method with serum modifications (4,5). In this method, arginase activity was determined using L-arginine as a substrate, and then the amount of urea from the arginase hydrolysis was determined using the thiosemicarbazide-diacetylmonoxime-urea (TDMU) method (6) spectrophotometrically at

520 nm. Urea accumulation proportionally reflects arginase activity.

NO measurement

In determining the concentration of nitrate + nitrite, nitrates are reduced to nitrites with nitrate reductase enzyme and the total nitrite concentration is measured. Nitrite measurements are a spectrophotometric measurement based on the Griess reaction (6). Phosphoric acid (H_3PO_4) in the Griess reagent reacts with the nitrite and nitrous acid occurs. The nitrous acid reacts with the sulfanilamide and diazobenzenesulfonic acid occurs. Reaction with naphthyl ethylenediamine causes the dark pink-colored complex (an azo compound). The color intensity of this compound is measured with a spectrophotometer.

Arginine measurement

The plasma arginine level was determined using the Agilent Hewlett Packard 1100 Modular System and the high-performance liquid chromatography (HPLC) method. First, 300 mL of plasma was adjusted with 200 mL of SERAPREP solution to a pH of 2.3. It was then centrifuged for 3 min at 10,000 rpm. The supernatant was measured by HPLC.

Statistical analysis

Statistical analysis of the data was performed using SPSS 11.0. Results were expressed as means ± standard deviations. First, the data were searched for normal distribution. Data with normal distribution were compared by independent t-tests. $P < 0.05$ was considered significant. The relationship between 2 different parameters was assessed by Pearson's correlation tests.

Results

No significant difference was found between the esophageal cancer patients and the control group for age and sex ($P > 0.05$). Of the patients, 78% of had squamous cell carcinoma and 22% had adenocarcinoma. Tumors were located in the upper third, middle third, and distal third of the esophagus in 7%, 45%, and 48% of the patients, respectively.

Mean arginase activity was measured as 10.4 ± 9.3 U/L and 7.5 ± 4.8 U/L in the patients and the control group, respectively. Arginase activity in the patient group was significantly higher than in the control group, with statistical significance ($P = 0.005$).

Mean NO levels were 16.2 ± 3.0 μmol/L and 10.1 ± 1.2 μmol/L in the patients and the control group, respectively. NO levels in the patient group were significantly higher than in the control group ($P = 0.0001$).

Mean arginine levels were 41.9 ± 13.4 μmol/L and 83.8 ± 26.8 μmol/L in the patients and the control group, respectively. Arginine levels in the patient group were significantly lower than in the control group ($P = 0.0001$).

Patients and controls were grouped according to sex and analyzed separately. Arginase activity, NO levels, and arginine levels were compared between the sexes in the patient group and control group and no statistically significant difference was found ($P > 0.05$) (Table 1).

Of the 100 patients in the study with esophageal cancer, there were 15 distant metastases (7 patients with liver metastasis, 6 patients with lung metastasis, and 2 patients with bone metastasis). Mean arginase activity in patients with and without metastases

Table 1. Sex distribution of the parameters in both groups.

Parameters	Patients with esophageal cancer		Control group		P
	Male	Female	Male	Female	
Arginase activity (U/L)	10.4 ± 8.2	10.7 ± 7.1	7.8 ± 4.3	7.2 ± 3.9	P > 0.05
NO level (μmol/L)	16.6 ± 4.3	15.8 ± 5.4	10.4 ± 1.9	9.8 ± 2.7	P > 0.05
Arginine level (μmol/L)	42.5 ± 11.9	41.4 ± 15.6	84.2 ± 22.4	81.8 ± 25.1	P > 0.05

was 10.1 ± 9.4 U/L and 8.1 ± 7.0 U/L, respectively. Arginase activity in patients with metastasis was higher, but no statistical significance was determined (P = 0.26).

While the mean NO levels in patients with distant metastases was 10.1 ± 5.3 mmol/L, the mean NO levels in patients without metastasis was 13.0 ± 4.1 mmol/L. NO levels in patients without metastasis were higher, but this was not statistically significant (P = 0.31).

The arginine levels in patients with and without distant metastases were 40.3 ± 11.3 mmol/L and 43.6 ± 25.7 mmol/L, respectively. Despite the high level of arginine in patients without metastasis, the difference was not statistically significant (P = 0.608).

Pearson's correlation test was performed for arginase activity, NO levels, and arginine levels. No significant correlation was found (P > 0.05).

No statistically significant difference was found for the measured arginase activity, NO levels, and arginine levels in patients with histopathologically different tumor types (Table 2).

Parameters were evaluated according to different locations of the tumor; however, no statistically significant difference was found (P > 0.05).

With the receiver operating characteristic (ROC) curve of arginase, arginine, and NO, sensitivity and specificity were calculated. While arginine showed low accuracy (field: 0.418) (P = 0.144), arginase (field: 0.765) (P < 0.0001) and NO (field: 0.875) (P < 0.0001) showed high accuracy. Therefore, the sensitivity and specificity were calculated for these 2 parameters. The sensitivity and specificity values, as cut-off values, are shown in Table 3.

Discussion

Many tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), squamous cell carcinoma (SCC) antigen, carbohydrate antigen 125 (CA 125), and carbohydrate antigen 50 (CA 50) have been used in early diagnosis and for monitoring the response to therapy in esophageal cancer. In most studies, especially in the diagnosis of the early stage esophageal cancer, these tumor markers were found to be of limited use (7).

Arginine significantly decreases in cancer patients with increasing arginase production, resulting in a decrease of T-cell proliferation and functional damage. However, the mechanism of inhibitor effects on T-cell proliferation in the case of arginine

Table 2. Distribution of the parameters by tumor type.

Parameters	Squamous cell cancer	Adenocarcinoma	P
Arginase activity (U/L)	9.8 ± 7.6	10.4 ± 6.6	P = 0.685
NO level (μmol/L)	15.6 ± 6.1	16.9 ± 3.2	P = 0.457
Arginine level (μmol/L)	43.7 ± 26.7	42.4 ± 28.3	P = 0.184

Table 3. Sensitivity and specificity of arginase and NO based on cut-off values.

	Arginase (U/L)			NO (μmol/L)		
Cut-off level	7.2	8.5	10.0	10.4	10.6	11.2
Sensitivity	87%	80%	72%	89%	83%	83%
Specificity	65%	65%	75%	66%	86%	86%

deficiency remains unclear (8). It has been shown that arginase activity in tumors induces arginine deficiency.

It has been shown that ongoing arginase activity in plasma may cause a decreased arginine concentration by up to 94% (9). Lamb et al. (10) showed that arginine deficiency disrupts the DNA synthesis phase of G1. Hester et al. (11) observed a significant reduction in tumor mass with arginine administration in mice with squamous cell carcinomas. Rodriguez et al. (12) demonstrated that mouse peritoneal macrophages stimulated with T-helper cytokines produced arginase; then the arginine concentrations decreased rapidly and the induction of T-cell dysfunction occurred.

Naini et al. (13), using age-matched control groups, found that arginine concentrations were low in patients with lung cancer but that there was no change in patients with esophageal cancer. In the present study, the samples were deproteinized and age/sex matches were taken into consideration. Arginine concentrations in patients with esophageal cancer were significantly lower than those of the control group ($P < 0.0001$). New studies are needed to clarify whether this depends on increased arginine uptake by the tumor or arginase secretion.

Recent studies have shown that arginase has an important role in tumor immunobiology. Increased arginase activity has been reported in different tumor types. It has been determined that a strong link is necessary between the proliferation of malignant cells and their production of arginase. This was explained by the relationship between the polyamine production and the support of the malignant cell proliferation (14).

In past studies, arginase activity was found to have a close association with various types of cancer, especially colorectal (15), prostate (16), pancreas (17), and stomach (18) cancer, where increased arginase activity has been demonstrated. Chrzanowska et al. (19), in their study population with hepatocellular carcinoma, observed that high arginase activity decreased after resectioning of the tumor. The relationship between the increased arginase activity in patients with malignant cells and polyamines has been considered, and cancer development might depend on increased polyamine synthesis. Therefore, it has been noted that arginase might be used as a biologic marker in the process of cancer development.

Wu et al. (20) investigated serum arginase activity in patients with peptic ulcer and gastric cancer and found that serum arginase activity was significantly higher in gastric cancer patients than in peptic ulcer patients or healthy individuals. There was no significant difference between the patients with peptic ulcer and the control groups. The same researchers also investigated the relationship between serum arginase activity and the stage of gastric cancer. The mean serum arginase activity in patients with early stage gastric cancer was significantly higher in the control group. Moreover, serum arginase activity was higher in the advanced stage of gastric cancer than in the early-stage gastric cancer and in the control group. Leu and Wang (15) investigated serum arginase activity in colorectal cancer patients. When compared to normal mucosal tissues, arginase activity was determined to be 2 times higher in the colorectal cancer tissues.

In a study of lung cancer, arginase activity and the relationship between the arginase activity and cell type and extrapulmonary metastasis was examined. Compared with the healthy control group, all of the patients with lung cancer, including small cell lung cancer and nonsmall cell lung cancer and patients with and without extrapulmonary metastasis, had significantly higher erythrocyte arginase activities. On the other hand, between the patients with nonsmall cell or small cell lung cancer and patients with or without metastases, no significant difference in terms of erythrocyte arginase activity was detected (21). Gökmen et al. (22), in patients with skin cancer, including basal cell and squamous cell cancer, found significantly higher ornithine and arginase levels. However, there was no significant difference in the levels of ornithine and arginase between squamous cell carcinoma and basal cell carcinoma. The present study showed increased arginase activity in patients with esophageal cancer compared to the healthy controls ($P = 0.005$). In addition, arginase sensitivity and specificity were 87% and 65%, respectively. This finding supports the data from other studies conducted with other cancer types, including the gastrointestinal system. However, no significant difference in arginase activity according to the distant

organ metastasis and cell type was found.

The carcinogenic effect of NO may arise by direct DNA and protein damage or the inhibition of the programmed cell death mechanism. NO also enhances tumor growth by stimulating tumor angiogenesis. NO plays a role in several steps of tumor angiogenesis, such as endothelial cell proliferation, vascular permeability, and angiogenic growth factor (23).

In the first report of NO expression of human tumor cells in 1991, Radomski et al. (24) reported NO expression in the primary tumor and lymph node metastases of colorectal adenocarcinoma. Calcium-independent NOS activity has been shown in both groups of cells. In the literature, it has been reported that increased production of nitric oxide has a critical role in the development of cancer cells by the stimulation of angiogenesis and increased mutations via the stimulation of free radicals and DNA damage (25).

Inducible nitric oxide synthase (iNOS) is an enzyme that catalyzes the formation of nitric oxide from arginine. iNOS release and activity results in high levels of NO production. NO production at physiological levels is important for mucosal function and contributes to the protective effects of gastrointestinal system cells. However, in patients with chronic inflammatory disease of the gastrointestinal tract such as ulcerative colitis and gastritis, increased iNOS release was observed (26).

In a study of breast cancer, a positive relationship was found between the breast cancer/metastases and iNOS (27). It has been reported that increased NO production levels contribute to the formation of metastasis in breast cancer by increasing angiogenesis. In the present study, NO levels in patients with esophageal cancer were found to be significantly increased compared with the control group ($P < 0.0001$). In addition, the NO sensitivity and specificity were calculated as 89% and 66%, respectively. NO levels in patients with distant metastases were higher than in patients without metastasis, but there was no statistical significance ($P = 0.31$).

Chen et al. (28) demonstrated that iNOS inhibitors suppress the development of chemically induced esophageal cancer in rats. This finding suggests that selective iNOS inhibitors can prevent the development of esophageal cancer. It is known that polyunsaturated ω-3 fatty acids, which inhibit NO, reduce the risk of colon cancer in humans and rats (29). It has been demonstrated that the inhibition of NO synthesis in patients with breast cancer decreased tumor vascularization and thus tumor growth (30).

In conclusion, in the present study, it was found that plasma arginine, arginase, and nitric oxide levels in patients with esophageal cancer were significantly different than those of the control group. This finding suggests that the arginase enzyme and NO play a role in the progression of esophageal cancer, and that arginase activity and NO levels might be used as markers for the diagnosis of esophageal cancer. Moreover, arginase and NO blocking agents, with the support of arginine, can improve esophageal cancer progression and treatment response. However, more comprehensive studies are needed.

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