ORIGINAL ARTICLE

Changes of Leptin, Leptin Receptor and Fatty Acids During Chemoradiotherapy in Patients with Esophageal Cancer

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ABSTRACT

Background. Esophageal cancer patients with substantial weight loss have the worst prognosis. Weight loss is often refractory to the nutritional support. The reasons for weight loss are multifactoral: esophageal stricture, frequent alcohol abuse, cancer related cachexia. It may be a consequence of metabolic changes mediated by cytokines, hormones and tumor-derived products. Leptin, a protein produced by adipocytes, is an important signaling molecule in energy regulation and the metabolism of fatty acids, and it can also augment tumor growth of various cancer cell lines. Polyunsaturated fatty acids intake may play an important role in the reversal of cancer-related weight loss. In this study we examined the nutritional status (pre-treatment weight loss, actual weight, BMI), serum levels of leptin, soluble leptin receptor, TNF-α, IGF-1 and plasma phosphatidylcholin fatty acids before treatment starts, after treatment starts and just before its completion.

Methods and Results. In the group of 38 patients (33 men, 5 women), mean age 58 years, a statistically significant mean pre-treatment weight-loss of 8 kg and significant mean weight loss of 2 kg after chemoradiotherapy was observed. Concurrent chemoradiotherapy led to transient elevation of serum leptin level despite weight loss during chemoradiotherapy. Significant changes in percentage distribution of fatty acids in plasmatic phosphatidyl-cholin were observed.

Conclusions. Our results show the possibility of the direct influence of chemoradiotherapy on body weight regulation in advanced esophageal cancer patients.

Key words: esophageal cancer, soluble leptin receptor, fatty acids, nutritional condition, concurrent chemoradiotherapy.

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INTRODUCTION

Patients with esophageal cancer have very bad prognosis even if radical surgery is performed. A combined therapeutic approach with preoperative chemoradiotherapy (CRT) and with subsequent resection may prolong survival, but it is linked with higher risk of postoperative mortality and morbidity. Weight loss of more than 10% of body weight during the 3-6 months preceding the diagnosis of cancer is considered an unfavorable prognostic factor (1). The successful completion of therapeutic process including radical operation implies the prevention of progressive weight loss and progressive nutritional deficit during chemoradiation (2). In clinical practice, in some patients we are unsuccessful in preventing progressive cachexia even in cases when vigorous and systematic nutritional support is part of the combined therapeutic procedure. Other factors may contribute to weight loss in addition to dysphagia due to the tumor: the size of the tumor, including produced cytokines, depression or adverse effects of therapy.

So far, the role of leptin in the mechanisms influencing body weight in patients with malignant tumors has not been fully elucidated. Leptin is a protein hormone produced predominantly by the adipocytes, which participates in the regulation of food intake and expenditure of energy. Leptin binding to the central leptin receptors in the hypothalamus leads to the inhibition of hypothalamic synthesis and to secretion of neuropeptide Y (NPY), a hormone that stimulates appetite and food intake and suppresses expenditure of energy (3). Remarkable changes in leptin concentrations appear mainly in conditions where the total content of fat in the organism is markedly changing. Malnutrition conditions, leading to a decrease in body fat content, are also mostly linked with a decrease of leptin serum levels. This occurs in patients suffering from mental anorexia, in patients with short intestine syndrome, with benign diseases of the alimentary tract etc. (4). In these cases, the change of leptin concentration is the consequence, not the cause, of malnutrition. So far, renal failure is the only known condition in which change of leptin concentration, within the meaning of hyperleptinemia, may

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be the causal factor of anorexia and malnutrition. Hyperleptinemia is probably caused by a combination of decreased secretion by the kidneys and increased expression and secretion of inflammatory cytokines in consequence of septic complications (5).

Serum leptin concentrations and their significance in the course of malignant disease still have not been fully elucidated. For example, hyperleptinemia was experimentally induced by increase of concentrations of TNF-α (6), IL-1 and IL-6 (7). According to our current understanding, these cytokines play a role in the mechanisms of development of tumor cachexia. The level of leptin may also be influenced by anti-tumor chemotherapy. In one trial, there was a significant rise in leptinemia (8) for several days after commencement of chemotherapy.

Leptin may also be related to cancerogenesis. The levels of leptin are elevated in obesity, which is a risk factor of some types of malignant tumors (breast cancer, colon cancer, prostate cancer, but also adenocarcinoma of distal esophagus) (9). In tissue culture experiments, the possibility of potentiation of tumor growth by leptin has been proved (10).

In this respect, there is an interesting influence of n-3 polyunsaturated fatty acids (PUFA) on leptinemia regulation in experimental animals. The leading representatives of n-3 PUFA are eicosapentaenic acid (EPA, 20:5n-3) and docosahexaenic acid (DHA, 22:6n-3), which have many favorable effects on the human organism (12). In experiments, potential anti-tumor activity of n-3 PUFA was found, based on the modulation of eicosanoid production, decrease of secretion of inflammatory cytokines, influence on angiogenesis, proliferation, apoptosis and metabolism of estrogens (13). In humans, n-3 PUFAs were successfully used in the suppression of tumor cachexia and in positively influencing the quality of life (14).

During cancerogenesis and tumor progression, various growth factors gain ground; one of them is IGF-1 factor (insulin-like growth factor-1) in esophageal cancer (15).

The aim of this pilot study was to follow the body weight, its changes and other indicators of nutritional conditions (serum leptin and its receptor), levels of TNF-α and IGF-1 and fatty acid composition in plasmatic phosphatidylcholin in patients with esophageal cancer during preoperative chemoradiotherapy.

MATERIAL AND METHODS

Thirty-eight patients with histologically proved squamous cell carcinoma or adenocarcinoma of the esophagus were treated with combined multimodal procedure comprising preoperative concurrent chemoradiotherapy (CRT) and subsequent resection. CRT consisted of a combination of 2 cycles of carboplatinum and paclitaxel with continuous infusion of 5-fluorouracil, administered during 6 weeks simultaneously with external megavoltage radiation therapy using dose 45 Gy in 25 fractions. The surgical operation was performed after 4-6 weeks, on the assumption that it is not contraindicated or refused by the patient. All patients were prospectively followed-up, and individual nutritional support was offered. The therapeutical protocol was approved by the institution and by the Ethics Committee of the 1st Medical Faculty of the Charles University and the General Teaching Hospital (Prague), and all patients signed the informed consent.

In all treated persons, loss of weight was monitored from the beginning of the symptoms (arbitrarily 6 months before the commencement of therapy). The current body weight, height, and body mass index (BMI) - calculated as weight/height^2 - were measured at the same time with blood taking before chemoradiotherapy commencement (entry), 7-10 days after the beginning of therapy (CRT 1) and then 4 weeks before the termination of treatment (CRT 2). Serum levels of leptin, soluble leptin receptor (SLR) and IGF-l (using commercial ELISA kits: BioVendor, CZ, Immunotech, CZ), were measured. Tumor necrosis factor alpha (TNF-α) was measured by commercial kit RSD Systems Inc., USA. The spectrum of fatty acids (FA) in plasmatic phospholipids was analyzed by means of capillary gas chromatography (16). The changes of individual serum parameters during therapy and their relations with nutritional data as body weight, BMI, and their changes, were followed.

Statistical analysis

All the statistical analyses were performed by means of programme Statistica, version 7.0 (Statsoft Inc., 2004) (17). For purpose of description of continuous parameters, mean values and standard deviations were calculated. Paired *t*-test was used for comparison of the values measured repeatedly during time. Correlation analysis was performed using Pearson's correlation coefficient. The differences of values of laboratory parameters between the patient groups were evaluated by unpaired *t*-test or by ANOVA. For evaluation of the relation between BMI and values of single laboratory parameters, correlation analysis or ANOVA were used. For purpose of evaluation of dissimilarities of laboratory parameters between the defined groups of patients in the course of time, ANOVA repeated measures test, augmented by paired and unpaired *t*-test, was used for more detailed analysis of the subgroups. All data were evaluated on level of significance α=5% and all used statistical methods were two-tailed. Normality of distribution was verified before using of parametric statistical methods.

RESULTS

Thirty-eight patients treated by protocol from 01/07/2003 till 30/03/2005 were evaluated. There were 33 males and 5 females, with a mean age 58.6 years (range 44–76). Squamous cell carcinoma was prevailing, it occurred in 33 cases, adenocarcinoma appeared in 4 cases and undifferentiated carcinoma in one patient. Average loss of body weight was 8 kg (10% of body weight), in the course of therapy further average decrease 2 kg (3%) being statistically significant (Tab.1).

In Tab. 2, changes of leptinemia, concentration of soluble leptin receptors, TNF-α, IGF-1 and fatty acids in plasmatic phosphatidylcholin during the treatment are indicated. The level of leptin during blood taking CRT 1 increased by 43%; nevertheless this difference, with respect of magnitude of variance, failed to reach the statistical significance (*t*-test P=0.210). During further treatment the level of leptin slightly decreased but still remained higher than on introductory examination (by 11%). The trend assessed by ANOVA was not statistically significant (P=0.210). Concentration of soluble leptin receptor (SLR) statistically significantly dropped during the treatment (ANOVA; P=0.001), up to 15% if input examination and examination at the end of chemotherapy were compared (*t*-test; P<0.001). TNF-α and IGF-1 levels did not change significantly during the treatment.

On evaluation of the changes of fatty acid concentrations in plasmatic phospholipids in the entire group of the patients during the treatment, statistically significant decrease of palmitic acid (16:0) after the commencement of CRT (P<0.05) was detected with ongoing decrease, but the trend assessed by ANOVA method (P=0.112) did not reach statistical significance. In case of concentrations of total saturated fatty acids (total SFA), their gradual decrease close to the border of statistical significance (P=0.068) was found. Then significant decrease of palmitoleic acid concentration (16:1 n-7) was observed in comparison of the input examination with the level after the first chemotherapy (CRT 1) and with concentration at the end of therapy (CRT 2) (both P<0.05), as well as trend evaluated by ANOVA test was significant (P=0.033). The same trends as in 16:1n–7 were observed in total monoenic fatty acids (total MFA), but statistical significance was proved only by *t*-test ENTRY versus CRT 1. On investigation of CRT 1, statistically significant increase of dihomogammalinoleinic acid (20:3n-3) (P<0.01) was observed, also ongoing during measurement CRT 2 (P<0.05), ANOVA test was also highly significant (P=0.003). Gradual marked increase (ANOVA; P<0.001) of concentrations of docosahexaenic acid

Tab. 1. Body weight, BMI and their change before therapy and during chemoradiotherapy

	N	BMI [1)]	Body weight (kg) [1)]	Changes of body weight and BMI	BMI [1)]	Body weight (kg [1)])	% [1)]	P
6 months before	38	26.9±4.6	81.4±14.4	6 months before vs ENTRY	-2.67 ±1.75	-8.12 ±6.36	-10±8	<0.001
ENTRY	38	24.2±4.4	73.3±13.8	6 months before vs CRT 2	-2.96 ±1.77	-8.93 ±6.75	-11±8	<0.001
CRT 1	38	23.6±4.4	71.4±13.3	ENTRY vs CRT 2	-0.65 ±1.43	-2.02 ±0.29	-3±0.3	0.02
CRT 2	26	23.0±4.2	68.8±12.0					

[1)] mean, ± standard deviation

Tab. 2. Changes of serum level of laboratory parameters and fatty acids in plasmatic phosphatidylcholin during concomitant chemoradiotherapy

Laboratory parameter	**Entry [1)]**	**CRT 1 [1)]**	**CRT 2 [1)]**	**ANOVA test (P)**
Leptinemia (ng/ml)	5.41±6.07	7.74±10.28	6.03±6.92	NS
SLR (U/ml)	28.60±10.47	25.69±12.93	24.25±8.31 [cc]	0.001
TNF-α (ng/ml)	1.41±0.89	1.31±0.78	1.40±1.66	NS
IGF-1 (μg/l)	225.91±124.96	254.07±154.36	260.90±125.48	NS
Fatty acid (mol %)				
14:0	0.22±0.07	0.21±0.07	0.22±0.08	NS
16:0	31.22±1.46 [a]	30.52±1.79	30.44±2.17 [III]	0.112 NS
18:0	13.35±1.32 [I]	13.75±1.39	13.56±1.62	NS
16:1n-7	0.80±0.44 [a]	0.68±0.30	0.72±0.42 [c]	0.033
18:1n-9	11.95±2.32 [a]	11.19±2.10	11.46±2.27	NS
18:2n-6	19.89±2.62	19.91±2.48	19.68±2.79	NS
18:3n-6	0.08±0.06	0.11±0.15	0.08±0.05	NS
20:3n-6	2.80±0.66 [aa]	3.23±0.76	3.14±0.71 [c]	0.003
20:4n-6	11.03±2.14	11.30±2.13	11.29±2.15	NS
18:3n-3	0.19±0.07	0.20±0.08	0.19±0.07	NS
20:5n-3	0.74±0.46	0.83±0.50	0.75±0.26	NS
22:6n-3	3.51±0.86 [a]	3.88±0.89	4.12±0.95 [cc]	<0.001
Total SFA	44.82±1.24	44.54±1.51 [II]	44.28±1.36 [IV]	0.084 NS
Total MFA	14.91±2.86 [a]	14.10±2.69	14.52±2.99	NS
Total n-3 PUFA	5.34±0.93 [a]	5.77±1.15	5.85±1.01 [c]	0.016
Total n-6 PUFA	34.91±2.96	35.60±2.38	35.46±2.17	NS
Ratio n-6/n-3	6.74±1.30	6.40±1.29	6.29±1.01	NS

[1)] mean, ± standard deviation
Significant difference and insignificant trend ENTRY versus CRT 1: [a] P<0.05, [aa] P<0.01, [I] p= 0.084; insignificant trend of CRT 1 versus CRT 2: [II] p=0.085; statistically significant difference and insignificant trend ENTRY versus CRT 2: [c] P<0.05, [cc] P<0.01, [III] p=0.08, [IV] p=0.068 (paired t-test).

(22:6n-3) was also interesting, being significant in CRT 1 (*t*-test; P<0.05) even at the end of the treatment (*t*-test; P<0.01). The same trend was also followed by concentrations of total n-3 PUFA. The differences of n-6/n-3 ratios were not statistically significant.

BMI was significantly correlated with the levels of leptin receptor, leptinemia and total saturated fatty acids (total SFA) (Tab. 3). The levels of leptin receptors were negatively correlated with input BMI value; the levels were lowest in the obese persons (Fig. 1). In total monounsaturated fatty acids (total MFA), the negative correlation was only close to the margin of statistical significance (P=0.068 in measurement ENTRY and P=0.055 in measurement CRT 1).

On investigation of relationship of the relative change of BMI to that of other examined parameters, statistically significant negative correlation between the change of leptinemia and BMI after the first chemotherapy was found (ENTRY vs. CRT 1) (R=-0.119; P=0.036).

The analysis of the changes of the values of parameters during the therapy in single groups of BMI (division of all patients into three equally numerous groups – tertiles based on recent BMI and on comparison of the outer tertiles T1 versus T3) showed statistically significant differences between the outer groups in parameters: leptin receptor (ANOVA P=0.033), leptinemia (P=0.002), total SFA (P=0.011), total MFA (P=0.019). The supplementary *t*-test showed significant if statistically borderline differences between the outer tertiles by BMI in each measurement, with the exception of SLR, where marked difference between group T1 versus T3 was proved only during measurement ENTRY (*t*-test, P<0.001), while both groups did not differ from each other during CRT 1 and CRT 2 measurements (Fig. 2, see Tab. 3).

DISCUSSION

The goal of this work was to follow the changes of body weight, serum leptin concentrations, soluble receptor and fatty acid compo-

Tab. 3. Relationship of laboratory parameters and BMI

Parameter	Measuring	Correlation with BMI [3]		I[st] tertile [1] (BMI<22.2)	III[rd] tertile [1] (BMI> 25.4)
		R	P	P [2]	P [4]
SLR (U/ml)	ENTRY	-0.573	0.005	36.91±10.88	21.05±6.85 [bbb]
	CRT 1	-0.332	NS	26.81±8.07	25.41±19.46
	CRT 2	-0.307	NS	27.41±9.40 [a]	20.77±8.31
Leptin (ng/ml)	ENTRY	0.767	<0.001	2.48±4.20	10.28±7.13 [bb]
	CRT 1	0.580	0.005	3.98±5.60	14.66±13.64 [b]
	CRT 2	0.622	0.002	3.52±6.98 [aa]	11.45±6.42 [b]
TNF-α (ng/ml)	ENTRY	-0.029	NS	1.56±0.89	1.35±0.87
	CRT 1	0.252	NS	1.23±0.88	1.37±0.65
	CRT 2	-0.285	NS	1.78±2.50	1.40±0.58
IGF-1 (μg/l)	ENTRY	0.119	NS	209.95±136.46	223.89±116.99
	CRT 1	-0.003	NS	249.68±106.47	245.56±178.93
	CRT 2	0.244	NS	224.05±118.23	284.74±135.97
Total SFA (mol%)	ENTRY	0.460	0.031	44.62±1.10	45.57±1.27 [b]
	CRT 1	0.625	0.002	43.89±1.68	45.27±1.06 [b]
	CRT 2	0.472	0.026	43.59±1.58 [a]	44.72±1.04 [l]
Total MFA (mol%)	ENTRY	-0.396	NS 0.068	16.65±3.53	14.42±1.94 [l]
	CRT 1	-0.415	NS 0.055	15.64±3.26	12.97±1.91 [b]
	CRT 2	-0.275	NS	16.05±3.80 [a]	13.41±1.91 [l]
Total PUFA n-6(mol%)	ENTRY	0.181	NS	33.56±2.94	34.44±2.74
	CRT 1	-0.002	NS	35.02±2.40	35.86±2.29
	CRT 2	0.064	NS	35.05±2.78	35.89±2.13
Total PUFA n-3(mol%)	ENTRY	0.113	NS	5.17±0.76	5.57±1.21
	CRT 1	0.268	NS	5.45±0.84	5.90±1.40
	CRT 2	-0.027	NS	5.73±1.30	5.75±0.94
n-6/n-3	ENTRY	0.043	NS	6.62±1.12	6.49±1.55
	CRT 1	-0.179	NS	6.56±1.10	6.37±1.37
	CRT 2	0.023	NS	6.59±1.34	6.35±0.79

[1] mean, ± standard deviation
[2] ANOVA test : statistically significant influence of BMI on time course of parameters I[st] tertile versus III[rd] tertile [a] P<0.05, [aa] P<0.01
[3] Pearson's correlation coefficient
[4] t-test : statistically significant difference of I[st] tertile vs III[rd] tertile [b] P<0.05, [bb] P<0.01, [bbb] P<0.001, [l] insignificant trend P<0.1

sition in plasmatic phosphatidylcholin (PC) among patients with esophageal cancer during the treatment by concomitant chemoradiotherapy.

There is an increasing trend of incidence of esophageal cancer in the Czech Republic (18), as with other countries (19), with obesity being among the risk factors, analogous to breast cancer, colon cancer and prostate cancer (20). Owing to the significant involvement of leptin in body weight regulation, the involvement of leptin in the pathogenesis of these malignancies is taken into consideration. The possibility of potentiation of tumor growth by leptin has been proved in tissue culture experiments (10). Leptin acts as mitogen in epithelial cells of the large intestine (21) and in breast cancer (22). Serum leptin in humans positively correlates with amount of adipose tissue and also with BMI (23-25).

We followed the sample of patients with advanced esophageal cancer, in whom pretreatment loss of body weight was 10% of body weight on average. The levels of leptin at entering the study were lower than average values found in the Czech population (26). After commencement of treatment (measurement CRT 1), the increase of leptinemia was detected (by 43%), though this did not reach the statistical significance with respect of the magnitude of variance. During the last examination, decrease of serum leptin concentration was observed; however, its level still surpassed the initial value (by 11%) despite the fact that the loss of weight continued in the course of treatment.

Literary data about leptin levels in malignancies vary. In some types of malignant tumors (breast cancer, colon cancer, prostate cancer but also adenocarcinoma of the lower esophagus) (9), higher levels of leptin have been proved. On the other hand, in patients with anorexia and cachexia, accompanying the advanced cases of tumors of gastrointestinal tract, mostly lowered or unchanged serum leptin concentrations have been found (27, 28). Usuki et al. (8) observed the rise in leptinemia during chemotherapy and deduced that chemotherapy might directly increase leptin secretion. The increased level of leptin causes decline of neuropeptide Y secretion in hypothalamus with subsequent loss of appetite and weight (3). These observations are compatible with our finding of statistically significant negative correlation between BMI change and leptinemia change at the beginning of chemotherapy (between examinations ENTRY and CRT 1).

Together with a rise in leptinemia during chemotherapy, a decrease of level of soluble leptin receptor was observed. This finding corresponds with literary data about reciprocal concentrations of SLR and serum leptin (29). The exact role of soluble leptin receptor in the organism has not yet been elucidated.

No significant changes of concentrations of TNF-α were observed during chemotherapy. This cytokine is one of the factors playing an active role in the development of tumor anorexia and cachexia (30), and at the same time, it is among the stimulants of leptin secretion (31). No significant changes of IGF-1 concentration occurred, either.

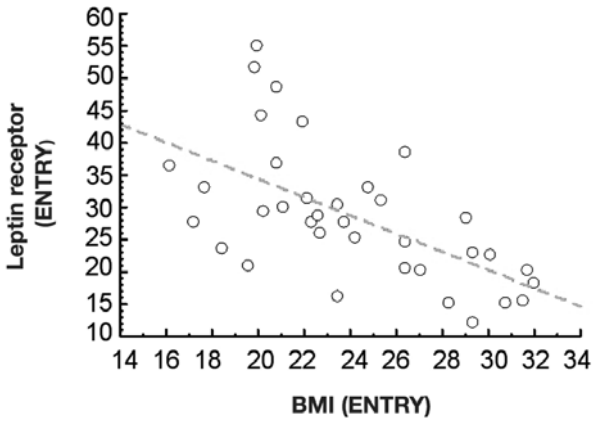

Fig. 1. Correlation of concentration of soluble leptin receptor and BMI on input blood taking
R= -0.573, P=0.005

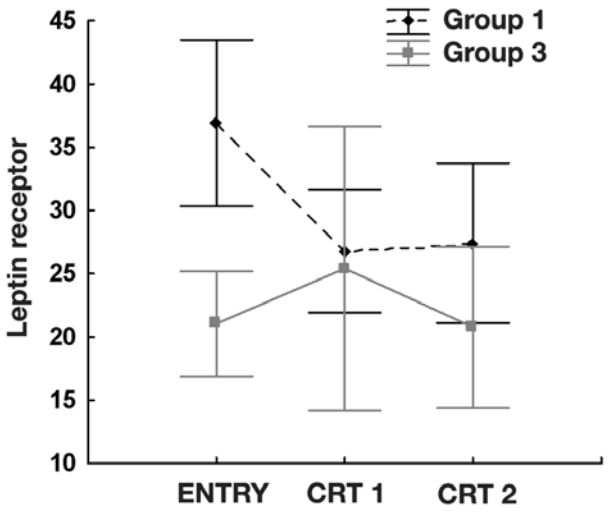

Fig. 2. Changes of concentration of soluble leptin receptor during CRT according to the different BMI of the treated patients
ANOVA; P=0.033
Group 1: BMI<22.2 (Ist tertile - T1), Group 3: BMI>25.4 (IIIrd tertile - T3)

Chemotherapy led to significant changes of fatty acid composition in plasmatic phosphatidylcholin (PC) in the sample of our patients with esophageal cancer. A significant decrease of palmitic acid (16:0) appeared, a decrease of total SFA, and also a significant decrease of portion of palmitooleic acid (16:1n-7) and a decrease of total MFA at the beginning of chemotherapy. These findings are consistent with lowered lipogenesis, corresponding with loss of weight (32). After division of the whole sample to tertiles according to BMI, we found that persons with higher BMI had higher concentration of leptin, which corresponds with the literary data (33), and they also have higher proportion of SFA at the expense of MFA, which can be explained by inhibitory activity of leptin towards stearoyl-CoA desaturase, which is a key enzyme in MFA synthesis, especially of oleic acid (18:1n-9) and palmitic acid (16:1n-7) (34).

Furthermore, during chemotherapy, we found an increase in the ratio of DHA and of total PUFA n-3, and an increase of concentration of dihommo-gammalinoleic acid (DGLA, 20:3n-6) in plasmatic PC. So far this finding has not been described in the patients with malignancy. Chemotherapy may influence the activity of hormone-sensitive lipase and selective preference during lipomobilization of the single fatty acids during decrease of body weight (35). Statistically significant increase of polyenic fatty acids, including PUFA n-3 in plasmatic PC, has been described in obese women, in whom weight-loss of 9% was maintained during one year after reducing diet (36).

For the present, the importance of this finding in patients after chemoradiotherapy cannot be evaluated. The rise in DHA content in the cells of intestinal carcinoma lowered their tendency to metastasizing (37). Owing to the increase of DHA content in phospholipids, the tumor cells might be more susceptible to lipoperoxidation and subsequent apoptosis (38). The increased content of PUFA n-3 suppressed angiogenesis in tumor tissue (39).

CONCLUSION

In conclusion, concomitant chemoradiotherapy in patients with advanced esophageal carcinoma led to a significant transient increase of serum leptin concentration and to a decrease in the level of soluble leptin receptor, despite the ongoing weight loss. Significant changes in representation of fatty acids in plasmatic PC occurred as well. We observed neither changes of concentrations of TNF-α, nor of IGF-1. The results indicate the possibility of the direct influence of chemoradiotherapy in the mechanisms of body weight regulation and nutritional state among patients with advanced esophageal carcinoma. Their analysis is being planned in relation to the therapeutical results (response to chemoradiotherapy, time to progression of the disease, survival), with the aim of formulating the prognostic and predictive factors for individualized selection of patients for multimodal therapeutical procedure.

Abbreviations

BMI	- body mass index
DGLA	- dihommo-gammalinoleic acid
DHA, 22:6n-3	- docosahexaenic acid
EPA, 20:5n-3	- eicosapentaenoic acid
FA	- fatty acids
CRT	- chemoradiotherapy
IGF-1	- insulin-like growth factor 1
IL-1, IL-6	- interleukin-1, interleukin-6
MFA	- monounsaturated fatty acids
NPY	- neuropeptide Y
PC	- phosphatidylcholin
PUFA	- polyunsaturated fatty acids
R	- correlation coefficient
SFA	- saturated fatty acids
SLR	- soluble leptin receptor
TNF-α	- tumor-necrosis-factor alpha

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