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Chemotherapy and plasma adipokines level in patients with colorectal cancer*

Wpływ chemioterapii na stężenie adypokin we krwi u pacjentów z rakiem jelita grubego

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A Study Design
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Summary

Adipokines are molecules produced and secreted by adipose tissue and are linked to multiple malignancies. Adipokines can suppress or promote particular cell behaviors in different types of cancer. The aim of this study was to investigate the impact of chemotherapy on select adipokines in patients with colorectal cancer (CRC).

Blood samples were collected from 42 patients with pathologically documented advanced CRC, who required palliative chemotherapy. Leptin, adiponectin, resistin and visfatin levels were measured by ELISA before and 3 months after the administration of chemotherapy. Among the 42 patients evaluated, 18 achieved a partial response (PR), 16 achieved stable disease (SD) and 8 patients experienced disease progression (PD).

We found that 5-fluorouracil-based chemotherapy regimens significantly increased plasma levels of leptin and adiponectin and decreased plasma levels of resistin and visfatin in PR and SD patients, whereas the plasma levels of these molecules were not affected in PD patients. Furthermore, the mean plasma levels of leptin were significantly lower, and the mean plasma levels of resistin and visfatin were significantly greater in patients with PD compared with PR and SD both before and after chemotherapy treatment.

We conclude that palliative chemotherapy in CRC patients, in addition to providing clinical benefits, positively affects cytokine production and secretion in PR and SD patients. Specifically, we found that palliative chemotherapy increased plasma levels of the anti-inflammatory adipokine adiponectin and decreased the plasma levels of visfatin and resistin, molecules known to promote angiogenesis and cancer cell proliferation in PR and SD patients. Moreover, the baseline values of leptin, visfatin and resistin might serve as prognostic indicators of a poor response to chemotherapy.

Key words: **adipokines • colorectal cancer • chemotherapy • adipose tissue • prognostic factor**

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Introduction

Globally, colorectal cancer (CRC) is the third most common type of cancer in males and the second most common cancer in females [12]. In addition to the influence of the increasing prevalence of obesity and the rising mortality rate of obesity-related disorders worldwide, hyperinsulinemia and insulin resistance are also likely to confer an increased risk of CRC. Thus, these conditions have increasingly drawn more attention in recent years. Notably, epidemiologic studies have revealed that obese or overweight individuals have an increased risk of colorectal adenoma and CRC [10]. Accordingly, diet-induced weight loss in obese individuals attenuates colorectal inflammation and markedly influences inflammatory and cancer-related gene pathways [34]. However, there is still a great deal of controversy regarding the precise mechanism of colorectal carcinogenesis in obese patients. Adipose tissue secretes a large quantity of bioactive molecules referred to as adipokines. Adipokines activate a variety of cell signaling pathways in central and peripheral tissues that modulate local and generalized inflammation and play a role in obesity-associated cardiovascular disorders (e.g., hypertension and atherosclerosis), diabetes and various cancers [6,36]. Among the various adipokines, adiponectin is the most abundant and accounts for 0.01% of the total plasma protein levels. Adiponectin inhibits the expression of vascular adhesion molecules, scavenger receptors and the pro-inflammatory cytokines TNFα, IL-6 and IL-1β in various tissues [1,41]. Moreover, the anti-inflammatory action of adiponectin is partly attributed to the induction and secretion of anti-inflammatory cytokines such as interleukin-10 (IL-10) [25]. Bråkenhielm et al. [5] demonstrated that adiponectin is also a negative regulator of angiogenesis. More precisely, in vitro, adiponectin potently inhibited endothelial cell proliferation and migration; in vivo, in the chick chorioallantoic membrane and the mouse corneal angiogenesis assays, adiponectin markedly inhibited new blood vessel growth via a mechanism involving the activation of caspase-mediated endothelial cell apoptosis. Furthermore, in a mouse tumor model, adiponectin significantly inhibited primary tumor growth.

Leptin is another adipokine thought to be associated with neoplasia. Leptin is primarily expressed in adipose tissue and exerts its actions through its receptor, OBR. Leptin's primary role is in controlling body fat stores. In contrast to adiponectin, circulating leptin levels are elevated in obese patients. Previous studies have revealed that leptin and/or OBR are overexpressed in carcinoma tissues compared with adjacent normal tissues and that leptin/OBR expression is directly correlated with the degree of malignancy in breast, endometrial, and gastric cancer [20,21,24]. Leptin signaling promotes VEGF expression, which synergistically stimulates angiogenesis to induce cancer growth and progression [17,46,48]. In summary, leptin appears to exert the opposite effects of adiponectin with respect to neoplasia-related mechanisms.

A related molecule, visfatin, is primarily synthesized and secreted by adipocytes and inflammatory cells (e.g., activated macrophages) as well as by other cells (e.g., hepatocytes) [8,16]. Visfatin was initially identified as an insulin mimetic secreted from visceral adipose tissue [14] and was characterized as a pre-β-cell colony-enhancing factor [37]. Visfatin essentially acts as a pro-inflammatory cytokine, capable of inducing the production of other cytokines, including IL-6 and TNFα [29]. Elevated circulating levels of visfatin have been observed in obese patients, individuals with metabolic syndrome (MS) and those who suffer from metabolic disorders such as diabetes mellitus and elevated visfatin levels might be related to the development of MS-related cancers [11,13].

Resistin, a member of the family of resistin-like molecules secreted from adipocytes, monocytes and macrophages in the peripheral blood, is another adipokine with pro-inflammatory features. Resistin exerts its pro-inflammatory effects by upregulating pro-inflammatory cytokines, most likely via the nuclear factor kappa-B (NF-κB) pathway [26]. In addition, resistin is able to stimulate the expression of cytokines, such as IL-6 [4], and adhesion molecules [43], most likely via toll-like receptor 4 [39]. Resistin is associated with various cancers including colorectal, prostatic, breast and endometrial cancers [2,18,23,40].

Although accumulating evidence suggests that adipokines play important roles in multiple types of cancer, there is a scarcity of data regarding adipokine behavior in the plasma of CRC patients undergoing palliative chemotherapy. Consequently, this study was designed to explore the association of plasma adipokine levels with patient clinical characteristics and the clinical response to chemotherapy in disseminated CRC.

Materials and Methods

Subjects

From January 2014 to July 2015, 42 patients with pathologically verified advanced CRC who required palliative chemotherapy were prospectively recruited in this pilot study. In total, 30 patients (71%) had previously undergone surgical treatment (tumor resection), but at the time of admission to the hospital, the disease was disseminated (T3/T4 with measurable metastases or nodal status up to N3). Overall, 12 patients (29%) were inoperable (unresectable metastases due to technical difficulties in 10 cases and unfavorable tumor characteristics in 2 cases). Among the 42 patients, 18 achieved a partial response (PR), 16 achieved stable disease (SD) and 8 experienced progressive disease (PD) following the course of chemotherapy. The exclusion criteria of this study included patients with diabetes mellitus or with acute and chronic infections. The clinical history of all patients was determined prior to their entry into the trial, and all the patients received a physical examination that included measurements of height, weight and body surface area. In addition, all patients underwent diagnostic laboratory tests to measure the levels of hemogram, sodium, potassium, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine and carcinoembryonic antigen CEA. A computed tomography (CT) or ultrasonography examination was performed shortly before admission (up to 28 days before) or on the day of admission. Patients who met the specified criteria received 6 cycles of chemotherapy with oxaliplatin and 5-fluorouracil (FOLFOX) or irinotekan and 5-fluorouracil (FOLFIRI). Following 6 courses of chemotherapy, the treatment efficacy was evaluated by radiological examination. Plasma levels of CEA were defined as an auxiliary parameter and were also measured. In addition, adipokines levels were reevaluated following the 6 weeks of treatment. The response rate (RR) was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), i.e., partial response (PR), stable disease (SD) and progressive disease (PD). No patients in this study achieved a complete response (CR).

Hormone and cytokine assays

A fasting blood sample was used for the adiponectin, leptin, resistin and visfatin assays. All samples were immediately centrifuged, and sera were separated and frozen at –20 °C until further use. Commercially

Tab. 1 Patients characteristics (n=42)

Sex	n		Chemotherapy	Mean value	Median value	Minimum	Maximum	25th quartile value	75th quartile value	Standard deviation (SD)
Male	28 (67%)	Age (years)	-	57.68	60.50	35.00	78.00	49.50	65.00	10.17
		Weight (kg)	-	75.03	73.00	51.30	117.00	66.00	82.20	13.82
		Hight (cm)	-	172.43	172.00	158.00	187.00	168.00	179.00	7.37
		BMI (kg/m2)	Before	25.14	25.51	18.91	36.52	22.18	26.77	3.70
			After	25.95	26.26	15.82	36.20	23.62	28.53	3.88
Female	14 (33%)	Age (years)	-	62.79	62.00	48.00	77.00	60,00	66.00	7.51
		Weight (kg)	-	64.55	63.30	53.50	83.00	55.50	69.50	9.45
		Hight (cm)	-	159.00	159.50	145.00	167.00	155.00	164.00	5.96
		BMI (kg/m2)	Before	25.63	26.18	19.90	33.42	21.36	28.06	4.13
			After	25.73	26.33	19.36	32.26	22.15	28.30	3.59
Total	42	Age (years)	-	59.38	61.00	35.00	78.00	56.00	65.00	9.59
		Hight (cm)	-	71.54	69.25	51.30	117.00	63.00	80.20	13.38
		Weight (kg)	-	167.95	168.00	145.00	187.00	161.00	175.00	9.39
		BMI (kg/m2)	Before	25.31	25.75	18.91	36.52	21.55	27.29	3.81
			After	25.87	26.31	15.82	36.20	23.50	28.39	3.74

Table 2. Leptin, adiponectin, resistin and visfatin plasma level in patients according to age and sergury (n=42)

Adipokines	Chemotherapy	Age Yes (n=30)			Sergury No (n=12)				
		R	p value		Mean value	SD	Mean value	SD	p value
Leptin (ng/ml)	Before	0.1337	0.399	R Spearman	9.79	1.78	9.70	0.81	0.697
	After	-0.0131	0.941		11.48	2.71	10.89	2.25	0.439
Adiponectin (µg/ml)	Before	-0.0443	0.781		9.19	4.29	15.05	3.17	<0.05
	After	0.1286	0.461		10.18	4.60	15.99	4.89	<0.05
Resistin (ng/ml)	Before	0.0257	0.872		9.957	4.28	8.96	3.49	0.626
	After	-0.1218	0.486		9.35	5.15	8.36	4.18	0.546
Visfatin (ng/ml)	Before	0.1167	0.462		2.08	0.66	1.89	0.50	0.578
	After	0.1869	0.282		1.93	0.73	1.74	0.65	0.534

U Mann-Whitney test

Table 3. Leptin, adiponectin, resistin and vistafin plasma levels according to gender (n=42)

Adipokines	Chemotherapy	Male (n=28)		Femal (n=14)		p value	
		Mean value	SD	Mean value	SD		
Leptin (ng/ml)	Before	9.48	1.45	10.35	1.63	<0.05	U Mann-Whitney test
	After	10.62	2.43	12.69	2.38	<0.05	
Adiponectin (µg/ml)	Before	11.23	5.32	10.14	3.53	0.904	
	After	12.01	5.95	11.04	3.82	0.986	
Resistin (ng/ml)	Before	10.26	4.43	8.51	3.00	0.205	
	After	9.90	5.47	7.55	3.12	0.231	
Visfatin (ng/ml)	Before	2.04	0.64	1.99	0.59	0.841	
	After	2.00	0.75	1.64	0.57	0.187	

available enzyme-linked immunosorbent assay kits (ELISA) were used according to the manufacturer's instructions to determine adiponectin, leptin, resistin and visfatin levels (Human Adiponectin, Human Leptin, Human Resistin, Human Visfatin; BioVendor, Laboratorni medicina a.s. Czech Republic). The absorbance measurements of all samples were obtained using the Universal Microplate Spectrophotometer (µQUANT BIOTEK Instruments Inc., Winooski, VT, USA) at a wavelength of 450 nm. The assay sensitivity for adiponectin was 0.26 ng/ml, and the intra- and inter-assay coefficients of variation (CV) were ≤5.9% and 6.3%, respectively. The assay sensitivity for leptin was 0.2 ng/ml, and the intra- and inter-assay CVs were ≤4.2% and 6.7%, respectively. The assay sensitivity for resistin was 0.02 ng/ml, and the intra- and inter-assay CVs were ≤5.2% and 7.0%, respectively. The assay sensitivity for visfatin was 0.016 ng/ml, and the intra- and inter-assay coefficients of variation were 5.58% and 6.24%, respectively.

Statistical analysis

Statistical analysis was performed using Statistica 10.0 PL software. The data were summarized descriptively as the mean, median, quartile, standard deviation, minimum and maximum values. Shapiro-Wilk's test was used to evaluate normality, and Levene's test was used to evaluate the homogeneity of variance. Statistical comparisons between groups were calculated with Student's t-test, Mann-Whitney U test and Kruskal-Wallis ANOVA. Dependent variables were analyzed using Wilcoxon's test. A Spearman non-parametric correlation was calculated. An alpha value with $p < 0.05$ was considered to be statistically significant.

Ethics statement

The study protocol was approved by the Bioethical Committee (reference KNW/022/KB1/69/12). Informed consent for this study was obtained from all patients.

Tab. 4a Leptin, adiponectin, resistin and visfatin plasma level in patients before and after 6 courses of chemotherapy treatment (n=42)

Adipokines	Before chemotherapy					
		Response			p value	
		PR (I)	SD (II)	PD (III)		
Leptin (ng/ml)	Mean value	10.37	10.34	7.28	I/II, I/III p <0.05	Kruskal-Wallis test
	Standard deviation (SD)	0.91	1.07	0.93		
Adiponectin (µg/ml)	Mean value	11.48	11.13	8.96	0.059	
	Standard deviation (SD)	6.03	4.22	3.33		
Resistin (ng/ml)	Mean value	8.12	8.22	16.06	I/II, I/III p <0.05	
	Standard deviation (SD)	2.33	2.66	3.25		
Visfatin (ng/ml)	Mean value	1.85	1.75	2.96	I/II, I/III p <0.05	
	Standard deviation (SD)	0.52	0.34	0.23		
	After chemotherapy					
	Response				p value	
		PR (I)	SD (II)	PD (III)		
Leptin (ng/ml)	Mean value	12.34	12.48	7.06	I/II, I/III p <0.05	
	Standard deviation (SD)	1.66	1.40	0.75		
Adiponectin (µg/ml)	Mean value	13.13	11.51	8.64	0.103	
	Standard deviation (SD)	6.06	4.41	3.72		
Resistin (ng/ml)	Mean value	6.89	7.25	17.30	I/II, I/III p <0.05	
	Standard deviation (SD)	2.30	2.08	3.92		
Visfatin (ng/ml)	Mean value	1.73	1.46	2.92	I/II, I/III p <0.05	
	Standard deviation (SD)	0.62	0.27	0.23		

Results

Patient demographic characteristics are summarized in Table 1.

There were no significant correlations between age and plasma levels of leptin, adiponectin, resistin or visfatin (Tab. 2). The BMI did not significantly differ between males and females before chemotherapy (25.14 ±3.70 vs. 25.63 ±4.13, respectively; p = 0.3895) or after chemotherapy (25.95 ±3.88 vs. 25.73 ±3.59, respectively; p = 0.8618). In addition, no significant changes in BMI before and after cancer therapy (regardless of gender) were observed (25.31 ±3.81 vs25.87 ±3.74, respectively; p = 0.493; data not shown in graphic form). Conversely, patients who had undergone tumor resection prior to chemotherapy induction exhibited significantly lower plasma adiponectin levels (both at the onset and conclusion of the study) compared with subjects who had not undergone surgical treatment (Tab. 2).

Several differences were observed between male and female patients with respect to leptin levels. Specifically, lower plasma levels of leptin were observed in males both before and after chemotherapy. No significant changes between genders were observed with respect to adiponectin, visfatin and resistin levels (Tab. 3).

Adipokines	Response	Before chemotherapy		After chemotherapy		*p* value	Change (%)	
		Mean value	SD	Mean value	SD			
Leptin (ng/ml)	PR	10.37	0.91	12.34	1.66	<0.05	19%	Wilcoxon signed-rank test
	SD	10.34	1.07	12.48	1.40	<0.05	21%	
	PD	7.28	0.93	7.06	0.75	0.447	-3%	
Adiponectin (µg/ml)	PR	11.48	6.03	13.13	6.06	<0.05	13%	
	SD	11.13	4.22	11.51	4.41	0.179	3%	
	PD	8.96	3.33	8.64	3.72	0.237	-4%	
Resistin (ng/ml)	PR	8.12	2.33	6.89	2.30	<0.05	-12%	
	SD	8.22	2.66	7.25	2.08	<0.05	-12%	
	PD	16.06	3.25	17.30	3.92	<0.05	7%	
Visfatin (ng/ml)	PR	1.85	0.52	1.73	0.62	<0.05	-6%	
	SD	1.75	0.34	1.46	0.27	<0.05	-16%	
	PD	2.96	0.23	2.92	0.23	0.499	-1%	

Table 5. Leptin, adiponectin, resistin and visfatin plasma level in patients before and after 6 courses of chemotherapy treatment (n=42)"

The mean level of leptin before chemotherapy in patients with PR and SD was 10.37 ±0.91 ng/ml and 10.34 ±1.07 ng/ml, respectively. Subjects with PD exhibited significantly lower leptin levels (7.28 ±0.93; p<0.05) compared with PR and SD patients prior to chemotherapy (Tab. 4a). Following 6 courses of treatment, the leptin levels increased significantly (p <0.05) in PR and SD subjects by 19% and 21% to 12.34 ±1.66 ng/ml and 12.48 ±1.40 ng/ml, respectively. Conversely, no significant changes in leptin levels (7.06 ±0.75 ng/ml; p = 0.447) from baseline values were observed in PD patients (Tab. 4b). Moreover, after chemotherapy, significant differences in leptin levels between patients with PR and PD (12.34 ±1.66 ng/ml vs. 7.06 ±0.75 ng/ml, respectively; p <0.05) or between patients with SD or PD (12.48 ±1.40 ng/ml vs. 7.06 ±0.75 ng/ml, respectively; p <0.05) persisted (Tab. 4a).

Adiponectin levels before chemotherapy did not significantly differ between PR, SD and PD subjects (11.48 ±6.03 µg/ml, 11.13 ±4.22 µg/ml and 8.96 ±3.33 µg/ml, respectively; p = 0.059) (Tab. 4a). Following 6 courses of treatment, adiponectin levels in PR patients increased by 13% to 13.13 ±6.06 µg/ml (p <0.05). Conversely, no changes in the SD or PD groups were observed following chemotherapy treatment (Tab. 4b).

In contrast to leptin and adiponectin, the resistin levels decreased significantly (p <0.05) in PR (by15%) and SD (by 12%) subjects from 8.12 ±2.33 ng/ml and 8.22 ±2.66 ng/ml to 6.89 ±2.30 ng/ml and 7.25 ±2.08 ng/ml, respectively. In PD subjects, a slight (7%) but significant (p <0.05) increase from 16.06 ±3.25 ng/ml to 17.30 ±3.92 ng/ml was observed (Tab. 4b). Furthermore, the baseline levels of resistin before chemotherapy in PR and SD patients were significantly lower (p <0.05) compared with PD patients (PR before: 8.12 ±2.33 ng/ml and after: 6.89 ±2.30 ng/ml; SD before: 8.22 ±2.66 ng/ml and after: 7.25 ±2.08 ng/ml; PD before: 16.06 ±3.25 ng/ml and after: 17.30 ±3.92 ng/ml, Tab. 4a).

Similar to resistin, the visfatin levels also decreased significantly (p <0.05) in PR (6% decrease) and SD (16% decrease) patients after 6 courses of chemotherapy from 1.85 ±0.52 ng/ml and 1.75 ±0.34 ng/ml to 1.73 ±0.62 ng/ml and 1.46 ±0.27 ng/ml, respectively. In PD patients, no significant changes were observed (2.96 ±0.23 ng/ml vs. 2.92 ±0.23; p = 0.499, Tab. 4b). Furthermore, the baseline levels of visfatin before and after chemotherapy in PR and SD patients were significantly (p <0.05) lower compared with PD patients (PR before: 1.85 ±0.52 ng/ml and after: 1.73 ±0.62 ng/ml; SD before: 1.75 ±0.34 ng/ml and after: 1.46 ±0.27 ng/ml; PD before: 2.96 ±0.23 ng/ml and after: 2.92 ±0.23 ng/ml, Tab. 4a).

Discussion

The main findings of the present study are as follows: (1) oxaliplatin and 5-fluorouracil or irinotecan and 5-fluorouracil chemotherapy administered to CRC patients increased plasma levels of leptin and adiponectin and decreased plasma levels of resistin and visfatin in PR and SD patients, whereas the plasma levels of these molecules were unaffected in PD patients, (2) the mean level of leptin before and after chemotherapy in patients with PR and SD was significantly elevated compared with that of PD patients, and (3) the plasma concentration of resistin and visfatin before and after chemotherapy in PR and SD patients was significantly lower compared with that of PD patients.

The physiological plasma concentration of adiponectin in healthy nonobese individuals falls in the range of 10 μg/ml to 13μg/ml [3,28]. Lower plasma levels of adiponectin are observed in patients with colorectal (approximately 8% lower) [45] and gastric cancers (approximately 30% lower) compared with matched controls [19]. One prospective nested case-control study revealed that plasma adiponectin levels were inversely associated with CRC risk in men [45]. Another study demonstrated an inverse relationship between adiponectin levels and the number and size of tumors. Together, this data suggests that adiponectin plays a protective role in cancer progression [33]. In this work, we found that a baseline level of adiponectin in PR patients of 11.48 μg/mL significantly increased by 13% to 13.13 μg/mL after 6 courses (3 months) of chemotherapy, results that are consistent with our previous findings [38]. Notably, these results are also consistent with those from a study by Umekawa et al. [42] that also demonstrated an increase in adiponectin levels (from 13.69 to 14.42 μg/mL, $p = 0.0092$) in patients with advanced non-small cell lung cancer treated for 30 days with tyrosine kinase inhibitors. Another study measured plasma concentration levels of adiponectin, leptin and resistin in children with acute lymphoblastic leukemia at diagnosis as well as during chemotherapy. Interestingly, they demonstrated that adiponectin levels significantly increased during chemotherapy, whereas leptin and resistin decreased from baseline values during chemotherapy. The results of this work confirmed the assumption that acute leukemia-related inflammation and plasma hyperlipidemia suppress adiponectin secretion and that adiponectin levels normalized during remission. In contrast, levels of the proinflammatory cytokines leptin and resistin declined as a result of the gradual attenuation of inflammation [30]. These observations are consistent with previous studies that reported higher levels of proinflammatory adipocytokines, such as leptin and resistin, in patients with cancer [22]. In our study, leptin levels increased, and resistin and visfatin plasma levels decreased in PR and SD patients. It should be noted that leukemia causes more severe inflammatory processes compared with malignancies of solid organs, such as metastatic CRC. This may, at least partially, account for the discrepancy (i.e., leptin changes) between our work and the results presented by the authors cited above [30].

Regardless of the fact that resistin seems to be involved in protracted inflammatory disorders (e.g. atherosclerosis) corresponding to its predominant expression in mononuclear cells [15], some case-control studies on the risk of myelodysplastic syndrome in patients with CRC have also been reported. Notably, Dalamaga et al. [9] demonstrated a decrease in resistin levels in patients with myelodysplastic syndrome, which they hypothesized might be a compensatory response to the up-regulation of other inflammatory factors etiologically linked to myelodysplasia. Conversely, others have demonstrated that resistin levels, particularly in CRC patients, were significantly greater than those in matched controls and that the concentration of resistin gradually increased with advancing tumor stage [32]. Other studies demonstrated that high plasma levels of visfatin were correlated with various cancers, such as malignant astrocytomas/glioblastomas, prostate cancer and gastric cancer [31,35,44]. Nakaijma et al. [32] found that, similar to resistin, visfatin levels were significantly elevated in CRC patients compared with that of controls and that resistin levels gradually increase with advancing tumor stage. Together, these findings suggest that resistin and visfatin are biomarkers of CRC malignancy and tumor stage progression. These findings indirectly support our observation that a marked decline in the plasma levels of resistin and visfatin was associated with a favorable clinical outcome (SD or PR). Conversely, no such effect (visfatin) or a completely opposite effect (resistin) was observed in patients with disease progression (PD patients).

Another important finding of the present study is that patients that did not respond to treatment (PD patients) had significantly lower plasma levels of leptin and higher plasma levels of resistin and visfatin compared with PR and SD subjects both before and after chemotherapy. This result implies that the adipokines leptin, resistin and visfatin might be prognostic factors for the chemotherapy response, although the limited number of cases in the PD group may limit the strength of this conclusion. A role for adipokines as prognostic indicators of the efficacy of cancer therapy has also been recently studied by Zemanova et al. [47]. They found that a high pretreatment level of serum adiponectin was associated with decreased overall survival in patients with squamous cell esophageal cancer that had received a multimodal regimen of concurrent neoadjuvant chemoradiotherapy followed by surgery.

In this work we also did not observe a significant correlation between age and adipokine levels; however, males exhibited lower plasma levels of leptin then females both before and after therapy. Similar gender differences in patients with at least one pathologically confirmed adenomatous colon polyp were demonstrated by Chia et al. [7]. In addition, patients who had previously undergone tumor resection prior to chemotherapy induction had significantly lower plasma adiponectin levels, both at the onset and the conclusion of this study, compared with subjects who had not undergo surgical treatment. This is at least partially in line with other studies demonstrating that plasma adiponectin levels decreased after CRC surgery [27].

Based on our preliminary results, we conclude that palliative chemotherapy in CRC patients, in addition to providing clinical benefits, positively influences cytokine production and secretion. Specifically, palliative chemotherapy in CRC patients increases the levels of the anti-inflammatory adipokine adiponec-

tin and decreases the levels of visfatin and resistin, molecules known to promote angiogenesis and cancer cell proliferation, in PR and SD patients. Moreover, the baseline values of leptin, visfatin and resistin might serve as indicators of a poor response to chemotherapy.

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