Nutrición Hospitalaria

Nutr Hosp. 2014;30(1):140-146
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original / *Cáncer*

The influence of nutritional status and disease on adiponectin and TNF-α levels in colorectal cancer patients

Mariana Abe Vicente[1], Tiago Donizetti Silva[2], Katia Barão[3], Aledson Vitor Felipe[4], Lila Oyama Missae[5] and Nora Manoukian Forones[6]

[1,2,3,4,6]*Departament of Medicine. Gastroenterology Division. Oncology Group. São Paulo. SP. Brazil.* [5]*Departament of Physiology. Physiology of Nutrition. São Paulo. SP. Brazil.*

Abstract

Background: **The aim of this study was to evaluate the association between adiponectin and tumor necrosis factor-α (TNF-α) serum levels in colorectal cancer (CRC) patients and compare these levels to clinical stage and nutritional status.**

Methods: **A total of 79 patients were enrolled in the study (39 with CRC and 40 in the control). Nutritional status was assessed by Patient-Generated Subjective Global Assessment (PG-SGA), body mass index (BMI), and phase angle (PhA). Adiponectin and TNF-α serum concentrations were determined using an enzyme-linked immunosorbent assay.**

Results: **Serum adiponectin levels were higher among CRC patients (p = 0.001). TNF-α serum levels were not significantly different between the groups, but patients with stage III or IV CRC had higher levels of TNF-α than those with lower stage disease (p = 0.037). The three tools used for the assessment of nutritional status (BMI, PhA, and PG-SGA) demonstrated that patients with a more severe nutritional deficit had higher adipocytokine levels, although these differences were significant only to TNF-α, when distributed PhA in tertiles.**

Conclusions: **Adiponectin levels were higher among CRC patients. Although TNF-α serum levels from CRC patients did not differ significantly to the control group, CRC patients with stage III or IV had higher levels compared to those with stage I and II tumors. Nutritional status, as determined by BMI, PhA, and PG-SGA, demonstrated that patients with a greatest nutritional deficit, had higher levels of adipocytokines; however, these differences were significant only for TNF-α, when distributed PhA in tertiles.**

(*Nutr Hosp.* 2014;30:140-146)

DOI:10.3305/nh.2014.30.1.7132

Key words: *Adipocytokines. Colorectal Cancer. Nutrition Assessment.*

Correspondence: Nora Manoukian Forones.
Disciplina de Gastroenterologia.
Universidade Federal de São Paulo.
R. Botucatu, 740 - 2º floor.
04023900 São Paulo. Brazil.
E-mail: marianaav@hotmail.com

Recibido: 12-XI-2013.
1.ª Revisión: 20-I-2014.
2.ª Revisión: 21-III-2014.
Aceptado: 22-IV-2014.

INFLUENCIA DEL ESTADO NUTRITIVO Y LA ENFERMEDAD SOBRE LAS CONCENTRACIONES DE ADIPONECTINA Y TNF-α EN PACIENTES CON CÁNCER COLORRECTAL

Resumen

Antecedentes: **El propósito de este estudio fue evaluar la asociación entre las concentraciones séricas de adiponectina y de factor de necrosis tumoral-α (TNF-α) en paciente con cáncer colorrectal (CCR) y comparar estas concentraciones con el estadio clínico y el estado nutritivo.**

Métodos: **Se reclutó a un total de 79 pacientes en el estudio (39 con CCR y 40 en el grupo control). Se evaluó el estado nutritivo mediante la Evaluación Global Subjetiva Generada por el Paciente (PG-SGA), el índice de masa corporal (IMC) y el ángulo de fase (AF). Se determinaron las concentraciones séricas de adiponectina y de TNF-α mediante un inmunoensayo de absorción ligado a enzima.**

Resultados: **Las concentraciones séricas de adiponectina fueron superiores en los pacientes con CCR (p = 0,001). Las concentraciones séricas de TNF-α no fueron significativamente distintas entre los grupos pero los pacientes con CC en estadios III o IV tuvieron mayores concentraciones de TNF-α que aquellos con un menor estadio de la enfermedad (p = 0,037). Las tres herramientas empleadas para evaluar el estado nutritivo (IMC, AF y PG–SGA) demostraron que los pacientes con un déficit nutricional más pronunciado presentaban mayores concentraciones de adipocitocina, aunque algunas diferencias sólo fueron significativas para el TNF-α cuanto se distribuyó el AF en terciles.**

Conclusiones: **Las concentraciones de adiponectina fueron superiores en pacientes con CCR. Aunque las concentraciones séricas de TNF-α de los pacientes con CCR no diferían significativamente de las del grupo control, los pacientes con CCR en estadios III o IV tuvieron concentraciones superiores en comparación con aquellos con tumores en estadios I y II. El estado nutritivo, determinado por IMC, AF y PG-SGA, demostró que los pacientes con un mayor déficit nutricional tenían concentraciones superiores de adipocitocinas; sin embargo, estas diferencias sólo fueron significativas para el TNF-α cuando el AF se distribuyó en terciles.**

(*Nutr Hosp.* 2014;30:140-146)

DOI:10.3305/nh.2014.30.1.7132

Palabras clave: *Adipocitocinas. Cáncer colorrectal Evaluación nutricional.*

Abbreviations

CRC: Colorectal cancer.
BMI: Body mass index.
PG-SGA: Patient-Generated Subjective Global Assessment.
SGA: Subjective Global Assessment.
PhA: phase angle.
TNF-α: Tumor necrosis factor-α.
TNM: Tumor-node-metastasis.
ELISA: Enzyme-linked immunosorbent assay.

Introduction

Colorectal cancer (CRC) has a complex etiology that includes the interaction of environmental and genetic factors. Recent studies reported that obesity is associated with an increased risk of CRC, although the mechanisms underlying this relationship remain to be fully elucidated[1]. Such mechanisms, however, include different distributions of body fat, alterations in hormonal status, obesity-related inflammation, and metabolic disturbances[2]. In particular, the increased adipose tissue in obesity causes an alteration of adipocytokine secretion, which may influence cancer initiation and progression[1,2]. Furthermore, there is evidence that several adipocytokines, (adiponectin, leptin, and TNF-α) have the potential to mediate the relationship between adiposity and colorectal neoplasma[3].

Tumor cells and tumor-associated leukocytes may also produce inflammatory cytokines such as TNF-α[4]. This cytokine has a possible role in all the steps involved in cancer initiation and progression, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis[4,5]. Additionally, TNF-α administration promptly lead to reduction of adiponectin expression and secretion[6]. Adiponectin may in turn induce anti-angiogenesis and anti-tumor activity[6]. Serum levels of adiponectin are associated with the activation of apoptotic enzymes in the caspase cascade, modulation of the expression of several apoptosis related genes in myelomonocytic cells, and reduction of tumor neovascularization[4].

Food intake and energy homeostasis are regulated by a complex network of peripheral mediators, including adipocytokines, changes in which can interfere with nutritional status[6]. Several studies demonstrated that adiponectin is inversely correlated with body weight.[7] and the decreased production of adiponectin in obese subjects can stimulate cancer progression through changes in insulin levels, inflammation, and angiogenesis[6-9]. However, the relationship between these cytokines or after weight loss in cancer patients has not been clearly established[7].

BMI, PhA, and PG-SGA are measures commonly used to determine nutritional status. BMI, which is easy to assess, has been the most widely used in epidemiological studies and clinical practice; however, it is relatively insensitive for the diagnosis of undernutrition[10-12]. PhA represents the electrical current stored by cell membranes[10], and its use has been studied in several diseases, including cancer[12,13]. The PG-SGA[14] is recommended as the standard method for the nutritional assessment of cancer patients by the Oncology Nutrition Dietetic Practice Group of the American Dietetic Association[15,16]. It identifies symptoms commonly seen during the treatment of cancer and includes a physical examination for the subjective assessment of nutritional status[16].

Some studies have demonstrated an association among adiponectin and TNF-α serum levels, nutritional status, and clinicopathological variables in CRC patients[17], but these studies involved heterogeneous patient groups and lacked a control group[7]. The aim of this study was to evaluate the association between adiponectin and TNF-α serum levels in CRC patients and determine if they are truly associated with the clinical stage and nutritional status.

Patients and methods

Subjects

This cross-sectional study involved outpatients treated by the Oncology Group from the Gastroenterology Division of the Federal University of Sao Paulo, between July 2010 and November 2011. The study was approved by the local Ethics Committee (Protocol 0826/10), and all patients signed an informed consent form. A total of 79 individuals were enrolled in the study, 39 of whom were CRC patients –the case group and 40 were healthy volunteers– the control group.

Data collection

Data on gender, age, treatment, site, and tumor stage were obtained from the medical records. The nutritional evaluation and collection of the blood sample for measuring adiponectin and TNF-α serum levels were performed at the same time. All patients were classified according to the tumor-node-metastasis (TNM) staging system[18].

BMI was calculated as weight (kg) divided by height (m^2). The subjects were classified according to the World Health Organization criteria[19] as undernourished (BMI < 18.5 kg/m^2), well nourished (BMI, 18.5-24.9 kg/m^2), and overweight/obese (BMI ≥ 25 kg/m^2).

The PhA was calculated as the ratio between resistance (R) and reactance (Xc), determined using the Biodynamics 450® bioimpedance analyzer with the standard protocol. R and Xc were measured directly in Ohms (Ω) at a single frequency of 50 kHz and 800 μA. The measurements were performed after at least 4 hours of fasting, with the patient lying in the supine position with his/her arms and legs extended to approxi-

mately 45° from the body. All procedures and controls for other variables affecting the validity, reproducibility, and precision of the measurements were performed according to the National Institutes of Health guidelines.[20] The PhA was calculated using the following equation: PhA = arctan (Xc/R) × (180/3.14).

The validated Portuguese version of the scored PG-SGA was used to assess nutritional status[21]. PG-SGA consists of two sections: in the first, information on weight history, food intake, nutrition impact symptoms, and functional capacity is collected, and in the second section, diagnosis, disease stage, age, components of metabolic demand (sepsis, neutropenic or tumor fever, corticosteroids), and physical examination were provided by the nutritionist. This analysis classified patients into three categories: (A) well-nourished, (B) moderately undernourished or suspected of being undernourished, and (C) severely undernourished.

Adipocytokine assays

Blood samples were collected in the morning in the fasting state. The serum samples were clotted and centrifuged at 2000 × *g* for 10 minutes and immediately frozen at –80° C for further analysis. Adipocytokine levels were measured using enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, MN, USA), adiponectin levels (with the sample diluted 4,000-fold) using the Duoset ELISA kit (DY1065), and TNF-α using the Quantikine ELISA kit (HSTA00D). The analytical methodology and technical procedures were performed according to the manufacturer's protocol.

Statistical analysis

The sample size had been calculated, considering the incidence of CCR in Brazil and the number of new cases in our Hospital.

Data are presented as percentages or mean ± SD. Differences between frequencies were assessed by chi-square test. Student's unpaired *t*-test and ANOVA test were used for normally distributed variables. Appropriate nonparametric tests (Mann Whitney *U*-test and Kruskal-Wallis test) were employed for all the other variables. The sample has been considered nonparametric for the study of adiponectin and TNF-alfa serum levels for the control and cancer group.

For the evaluation of PhA, a cutoff value was established for the population studied because of the lack of specific values for cancer patients. The PhA was divided by the distribution measured according to the proportion of observed frequencies for both groups. The data were separated into tertiles and values of the first tertile were defined as predictors of undernutrition. The analysis of variance was used to compare the classification of these tertiles for each group.

SPSS 20.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis, and values of $p < 0.05$ were considered statistically significant.

Results

There was no statistically significant difference with respect to gender, age and BMI between the groups. The majority of CRC patients had stage IV tumors (53.8%); 51.3% were not treated, 46.2% were undergoing chemotherapy, and 41% had undergone surgery for tumor resection (table I).

The mean serum levels of adiponectin were higher in CRC patients ($p = 0.001$) while TNF-α serum levels were similar between the groups ($p = 0.259$). Tumor stages I and II were analyzed together due to the small proportion of patients with stage I tumors. Compared to patients with stages I and II tumor, those with stage III or IV tumors had higher levels of TNF-α ($p = 0.037$) (table II).

The prevalence of moderate or severe undernutrition, as determined using the PG-SGA, was 69.2% in the case group. Only 7.7% of the CRC patients were undernourished as per their BMI, and none of the control group individuals were undernourished. No significant differences were found between the groups on

Table I
Characteristics of the patients in both groups

Parameters		*Case group*	*Control group*	*p*
Age	(yr ± SD)	61.0 ± 10.6	60.4 ± 9.2	0.765
Gender	Male	25 (64.1)	26 (65)	0.879
N (%)	Female	14 (35.9)	14 (35)	
Stage	I	2 (5.2)		
N (%)	II	5 (12.8)		
	III	11 (28.2)		
	IV	21 (53.8)		
BMI (mean ± SD)		23.9 ± 3.3	23.9 ± 2.4	0.893

Table II
Adiponectin and TNF-α segum levels among the groups and mean values according to the stage of disease for case group

Adipocytokine	*Case group (mean ± SD)*	*Control group (mean ± SD)*	*p**	*STAGE I and II mean ± SD*	*STAGE III and IV mean ± SD*	*p**
Adiponectin (μg/mL)	4.6 ± 2.1	3.6 ± 2.5	0.001	3.9 ± 1.1	4.8 ± 2.3	0.314
TNF-α (pg/mL)	3.7 ± 7.3	3.6 ± 5.1	0.259	1.2 ± 0.7	4.2 ± 7.9	0.037

* Mann Whitney.

the basis of PhA, although more subjects in the case group were in the first tertile (table III).

The mean of adiponectin (p = 0.337) and TNF-α (p = 0.128) levels was higher in undernourished cancer patients than in the other subjects; however, these differences were not significant. Difference on adiponectin level was observed between the groups according to the BMI classification only among the normal weight subjects (p = 0.009) (table IV).

The mean serum level of adiponectin (p = 0.073) and TNF-α (p = 0.005) in the case group was higher among patients in the first tertile of PhA; however, these differences were significant only TNF-α (table V).

Furthermore, based on the PG-SGA, there was no difference in adipocytokine levels between groups, even with the higher number of patients judged to be moderately or severely undernourished by this method (table VI).

Table III
Nutritional assessment results: BMI categories, Patient-Generated Subjective Global Assessment (PG-SGA) categories and phase angle in both groups

Parameters	*Case group*	*Control group*	*p*
BMI (kg/m²)	N (%)	N (%)	0.062
Undernourished (<18.5 kg/m²)	3 (7.7)	0 (0)	
Normal weight (18.5-24.9 kg/m²)	21 (53.8)	30 (75.0)	
Overweight/Obesity (≥ 25 kg/m²)	15 (38.5)	10 (25.0)	
PG – SGA	N (%)		
Severely Undernourished	3 (7.7)		
Moderately Undernourished	24 (61.5)		
Well Nourished	12 (30.8)		
Phase Angle	Mean ± SD (N)		
First tertile	5.1 ± 0.6 (n = 20)	6.0 ± 0.4 (n = 5)	0.161
Second tertile	6.4 ± 0.3 (n = 11)	6.8 ± 0.1 (n = 15)	0.294
Thirth tertile	7.6 ± 0.4 (n = 8)	7.8 ± 0.6 (n = 20)	0.794

Table IV
Adiponectin and TNF-α serum levels in both groups according to the BMI classification

BMI		*Case group mean ± SD*	*Control group mean ± SD*	*p**
Undernourished (<18.5 kg/m²)	Adiponectin	6.4 ± 1.7 (n = 3)		
	TNF-α	9.8 ± 14.8 (n = 3)		
Normal weight (18.5-24.9 kg/m²)	Adiponectin	4.3 ± 1.3 (n = 21)	3.6 ± 2.7 (n = 30)	0.009
	TNF-α	2.3 ± 1.8 (n = 21)	4.1 ± 5.8 (n = 30)	0.559
Overweight/Obesity (BMI ≥ 25 kg/m²)**	Adiponectin	4.8 ± 2.9 (n = 15)	3.4 ± 1.7 (n = 10)	0.292
	TNF-α	4.4 ± 9.8 (n = 15)	2.2 ± 1.9 (n = 10)	0.375

**The maximum value observed was 32,8 kg/m² in Case Group and 29,5 kg/m² in Control Group.
* Mann Whitney.

Table V
Adiponectin and TNF-α serum levels and percentiles of PhA in both groups

PhA		*Case group mean ± SD*	*Control group mean ± SD*	*p**
First tertile	Adiponectin	5.2 ± 2.5 (n = 20)	6.2 ± 5.5 (n = 5)	0.634
	TNF-α	5.9 ± 9.7 (n = 20)	3.5 ± 4.1 (n = 5)	0.812
Second tertile	Adiponectin	4.10 ± 1.1 (n = 11)	3.26 ± 2.0 (n = 15)	0.411
	TNF-α	1.3 ± 0.7 (n = 11)	5.1 ± 7.5 (n = 15)	0.055
Third tertile	Adiponectin	3.9 ± 1.8 (n = 8)	2.9 ± 1.2 (n = 20)	0.172
	TNF-α	1.2 ± 0.7 (n = 8)	2.6 ± 2.6 (n = 20)	0.036

* Mann Whitney.

Table VI
Adiponectin and TNF-α according to the PG-SGA in case group

PG-SGA		*Case group mean ± SD*	*p**
Well nourished	Adiponectin	4.9 ± 3.3 (n = 12)	0.762
Moderately undernourished	Adiponectin	4.4 ± 1.2 (n = 24)	
Severely undernourished	Adiponectin	5.3 ± 2.7 (n = 3)	
Well nourished	TNF-α	4.4 ± 10.8 (n = 12)	0.225
Moderately undernourished	TNF-α	2.4 ± 2.4 (n = 24)	
Severely undernourished	TNF-α	10.3 ± 14.5 (n = 3)	

*Kruskal-Wallis.

Discussion

To our knowledge, this is the first study to investigate the relationship between nutritional status determined using 3 different parameters (BMI, PhA, and PG-SGA) and serum levels of adiponectin and TNF-α in CRC patients. Among the CRC patients, the adipocytokine levels were also compared with the clinical stage.

We found that patients in the case group had higher serum levels of adiponectin. When compared to BMI, this difference was observed in patients with normal weight. Gonullu et al[22], in contrast, reported a lower level of adiponectin in CRC patients than in a control group (5.5 ± 5.2 μg/mL *vs* 6.2 ± 3.0 μg/mL, p = 0.030), although these groups exhibited no overall difference in BMI. These differences among the studies might reflect a higher proportion of undernourished individuals in the case group included in our study, and the inclusion of individuals with morbid obesity in the study of Gonullu et al.[22]

Adiponectin serum levels are inversely correlated with body weight in non-cancer patients, with low levels commonly observed in obese subjects[7,8]. Hillenbrand et al[8] found lower levels of adiponectin in obese patients without cancer, compared to those with CRC. Low adiponectin levels have also been described in advanced lung cancer patients with severe weight loss[9]. However, this correlation between weight loss in patients with lung or intestine cancer and adiponectin levels described by these authors[8,9] was not confirmed in a further independent study[17]. In our study, the adiponectin levels were higher in malnourished CRC patients, as classified by BMI, compared to those with a BMI ≥ 18.5 mg/m^2, but this difference was not statistically significant. The means were not compared for different categories within the control group because there were no undernourished control subjects. The different findings of our study and some previously published studies might be due to the different nutritional status of the enrolled patients.

We also found that patients with a stage III or IV tumor had higher serum adiponectin levels than patients with stage I and II tumors, although this difference was not significant. Gonullu el al [22] found higher serum levels of this adipokine in stage II cancer patients than in those with stage IV tumors (7.58 ± 5.0 μg/mL *vs* 1.92 ± 2.09 μg/mL). In contrast, Kumor et al[6] did not find an association between the serum concentration of adiponectin and the clinical stage.

TNF-α is considered an important promoter of various cytokines, and it has a known role in chronic inflammation, angiogenesis, tissue remodeling, tumor growth, and metastasis[23,24]. Paradoxically, this cytokine may also have a pro-apoptotic action, promote inhibition of tumor angiogenesis, and activate anti-tumor im-

munity[4]. Studies have shown that excess TNF-α can cause organ dysfunction and progression of cancer, including gastrointestinal tumors.[4,25,26] TNF-α increases lipolysis in adipocytes and consequently, the levels of circulating free fatty acids.[27] An overweight condition represents an expansion of the adipose tissue with an increased production of inflammatory factors and cytokines, especially TNF-α, which plays an important role in the pathophysiology of obesity.[4,26] In this study, we found no significant difference in serum TNF-α levels between the groups, in agreement with the findings of a previous study[28], although Guadagni et al[29] found higher serum levels of TNF-α in cancer patients.

We also found that serum values of TNF-α were higher among patients with advanced disease (stage III and IV). These findings were similar to those described by Guadagni et al[29], who also found higher TNF-α levels in patients with metastatic CRC. These results confirm that TNF-α may be involved in cancer progression.[8] In findings similar to those for adiponectin, TNF-α serum levels in malnourished CRC patients were also higher, although not significantly higher, than those in the non-cancer controls. Similarly, Hillenbrand et al[8] found a slight but not statistically significant elevation of TNF-α in CRC patients with a median BMI ≤ 27.1 kg/m^2 compared to obese or healthy controls.

In addition to the BMI, adipokine levels also associated with PhA and PG-SGA. PhA has been shown to provide a good estimate of the body compartment and can be used as a nutritional marker[30,31]. The levels of adiponectin and TNF-α with respect to different tertiles showed that the cancer patients in the first tertile had higher levels of adiponectin, however only TNF-α levels were significant. Similar findings were observed in relation to BMI, whereby malnourished patients had higher levels of adipokines; however, these differences were not statistically significant. These results suggest that worse nutritional status may cause higher levels of adiponectin and TNF-α.

A recent study in our institution using PG-SGA found that this was the method with a higher sensibility for determining nutritional status in CRC patients[32]. However when analyzed the PG-SGA classification with adipocytokines, no differences were observed among the groups, although these adipocytokines in undernourished patients was higher than in well nourished. Correia et al[33] reported that gastric cancer patients with TNF-α serum levels in excess of 8.72 pg/mL had a higher risk of malnutrition, according to the PG-SGA.

This study has some limitations, including the small number of CRC patients and the inclusion of underweight subjects in the case group. Although the control group consisted of individuals without cancer or gastrointestinal disease, the mean age of these subjects, matching that of the case group, may have favored the inclusion of individuals with inflammatory conditions, such as atherosclerosis and type II diabetes, which can also affect the serum levels of adipokines. The differences between serum levels of adiponectin and TNF-α in some studies may be a consequence of the variation of this cytokine with clinical stage and body weight.

In summary, the serum level of adipocytokine may be elevated in CRC patients, and we found that serum adiponectin levels were higher among CRC patients. TNF-α serum levels did not differ significantly between CRC patients and control subjects, but patients with stage III or IV CRC had higher levels compared to those with stage I and II tumors. The three measures used to indicate nutritional status (BMI, PhA, and PG-SGA) demonstrated that patients with a greater nutritional deficit had, on an average, higher levels of adipocytokines; however, these differences were not significant. Further studies with a greater number of patients are necessary to fully elucidate the relationship between adiponectin and TNF-α levels and the nutritional status and disease stage of CRC patients, and to determinate the pathophysiological role of adipokines in this cancer.

Conflict of Interest Statement

The authors have not declared any conflicts of interest.

Acknowledgements

This study was supported by the São Paulo Research Foundation (FAPESP, grant 10/19191-2). The authors thank the volunteers who participated in this study.

References

1. Siegel EM, Ulrich CM, Poole EM, Holmes RS, Jacobsen PB, Shibata D. The effects of obesity and obesity-related conditions on colorectal cancer prognosis. *Cancer Control*. 2010; 17 (1): 52-7.
2. VanKruijsdijk RC, Van Der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol Biomarkers Prev* 2009; 18 (10): 2569-78.
3. Hopkins MH, Flanders WD, Bostick RM. Associations of circulating inflammatory biomarkers with risk factors for colorectal cancer in colorectal adenoma patients. *Biomark Insights* 2012; 7: 143-50.
4. Nicholas J. Roberts, Shibin Zhou, Luis A. Diaz, Jr., Matthias Holdhoff. Systemic use of tumor necrosis factor alpha as an anticancer agent. *Oncotarget* 2011; 2 (10): 739-51.
5. Kim KY, Kim JK, Jeon JH, Yoon SR, Choi I and Yang Y: c-Jun *N*-terminal kinase is involved in the suppression of adiponectin expression by TNF-alpha in 3T3-L1 adipocytes. *Biochem Biophys Res Commun* 2005; 327 (2): 460-7.
6. Kumor A, Daniel P, Pietruczuk M, Małecka-Panas E. Serum leptin, adiponectin, and resistin concentration in colorectal adenoma and carcinoma (CC) patients. *Int J Colorectal Dis* 2009; 24 (3): 275-81.
7. An W, Bai Y, Deng SX, Gao J, Ben QW, Cai QC et al. Adiponectin levels in patients with colorectal cancer and adenoma: a meta-analysis. *Eur J Cancer Prev* 2012; 21 (2): 126-33.
8. Hillenbrand A, Fassler J, Huber N, Xu P, Henne-Bruns D, Templin M et al. Changed adipocytokine concentrations in colorectal tumor patients and morbidly obese patients compared to healthy controls. *BMC Cancer* 2012; 23; 12: 545.
9. Jamieson NB, Brown DJ, Michzel Wallace A, McMillan DC. Adiponectin and the systemic inflammatory response in weight-losing patients with non-small cell lung cancer. *Cytokine* 2004; 27 (2-3): 90-2.

10. Li H, Yang G, Xiang YB, Gao J, Zhang X, Zheng W et al. Body weight, fat distribution and colorectal cancer risk: a report from cohort studies of 134 255 Chinese men and women. *Int J Obes (Lond)* 2012; Sep 18.
11. Thibault R, Genton L, Pichard C. Body composition: Why, when and for who? *Clin Nutr* 2012; 31 (4): 435-47.
12. Llames L, Baldomero V, Iglesias ML, Rodota LP. Values of the phase angle by bioelectrical impedance; nutritional status and prognostic value. *Nutr Hosp* 2013; 28 (2): 286-95.
13. Kyle UG, Soundar EP, Genton L, Pichard C. Can phase angle determined by bioelectrical impedance analysis assess nutritional risk? A comparison between healthy and hospitalized subjects. *Clin Nutr* 2012; 31 (6): 875-81.
14. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition* 1996; 12 (Supl. 1): S15-9.
15. Ottery FD. Patient-Generated Subjective Global Assessment. In: The Clinical Guide to Oncology Nutrition, ed. PD McCallum & CG Polisena. *The American Dietetic Association* 2000. pp. 11-23.
16. Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr* 2002; 56 (8): 779-85.
17. Kim HJ, Kim HJ, Yun J, Kim KH, Kim SH, Lee SC et al. Pathophysiological role of hormones and cytokines in cancer cachexia. *J Korean Med Sci* 2012; 27 (2): 128-34.
18. Sobin LH, Gospodarowicz MK, Wittekind Ch (eds): TNM Classification of Malignant Tumours (ed 7). West Sussex, United Kingdom, Wiley-Blackwell, 2009.
19. Organización Mundial de la Salud. El estado físico: uso e interpretación de la antropometría. Genebra: OMS; 1995. p. 452.
20. [No authors listed]. NIH Consensus statement. Bioelectrical impedance analysis in body composition measurement. National Institutes of Health Technology Assessment Conference Statement. December 12-14, 1994. *Nutrition* 1996; 12 (11–12): 749-62.
21. Gonzalez MC, Borges LR, Silveira DH, Assunção MCF, Orlandi SP. Validação da versão em português da avaliação subjetiva global produzida pelo paciente. *Rev Bras Nutr Clin* 2010; 25 (2): 102-8.
22. Gonullu G, Kahraman H, Bedir A, Bektas A, Yücel I. Association between adiponectin, resistin, insulin resistance, and colorectal tumors. *Int J Colorectal Dis* 2010; 25 (2): 205-12.
23. Balkwill F. Tumour necrosis factor and cancer. *Nat Rev Cancer* 2009; 9 (5): 361-71.
24. Li B, Vincent A, Cates J, Brantley-Sieders DM, Polk DB, Young PP. Low levels of tumor necrosis factor alpha increase tumor growth by inducing an endothelial phenotype of monocytes recruited to the tumor site. *Cancer Res* 2009; 69 (1): 338-48.
25. Grimm M, Lazariotou M, Kircher S, Höfelmayr A, Germer CT, von Rahden BH et al. Tumor necrosis factor- is associated with positive lymph node status in patients with recurrence of colorectal cancer—indications for anti-TNF-α agents in cancer treatment. *Anal Cell Pathol (Amst)* 2010; 33 (3): 151-63.
26. Ren L, Zhu D, Wei Y, Pan X, Liang L, Xu J et al. Enhanced Recovery After Surgery (ERAS) Program Attenuates Stress and Accelerates Recovery in Patients After Radical Resection for Colorectal Cancer: A Prospective Randomized Controlled Trial. *World J Surg* 2012; 36: 407-14.
27. Zhang HH, Halbleib M, Ahmad F, Manganiello VC, Greenberg AS. Tumor necrosis factor-alpha stimulates lipolysis in differentiated human adipocytes through activation of extracellular signal-related kinase and elevation of intracellular cAMP. *Diabetes* 2002; 51 (10): 2929-35.
28. Yamaji T, Iwasaki M, Sasazuki S, Tsugane S. Interaction between Adiponectin and Leptin Influences the Risk of Colorectal Adenoma. *Cancer Res* 2010; 70 (13): 5430-7.
29. Guadagni F, Roselli M, Martini F, Spila A, Riondino S, D'Alessandro R et al. Prognostic significance of serum adipokine levels in colorectal cancer patients. *Anticancer Res* 2009; 29 (8): 3321-7.
30. Gupta D, Lis CG, Dahlk SL, King J, Vashi PG, Grutsch JF et al. The relationship between bioelectrical impedance phase angle and subjective global assessment in advanced colorectal cancer. *Nutr J* 2008. pp. 7-19.
31. Norman K, Stobäus N, Zocher D, Bosy-Westphal A, Szramek A, Scheufele R et al. Cutoff percentiles of bioelectrical phase angle predict functionality, quality of life, and mortality in patients with cancer. *Am J Clin Nutr* 2010; 92 (3): 612-9.
32. Abe Vicente M; Barão K, Silva TD, Forones NM. What are the most effective methods for assessment of nutritional status in outpatients with gastric and colorectal cancer. *Nutr Hosp* 2013; 28 (3): 585-91.
33. Correia M, Cravo M, Marques-Vidal P, Grimble R, Dias-Pereira A, Faias S et al. Serum concentrations of TNF-alpha as a surrogate marker for malnutrition and worse quality of life in patients with gastric cancer. *Clin Nutr* 2007; 26 (6): 728-35.