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Original Article / Orijinal Araştırma

Investigation of the Effect of Serum Leptin, Adiponectin, Resistin, C Peptide, IL-10, IL-22, and Visfatin Levels on Survival in Patients with Advanced Gastric and Colon Cancer

Serum Leptin, Adiponektin, Resistin, C Peptid, IL-10, IL-22 ve Visfatin Düzeylerinin İleri Evre Mide ve Kolon Kanserli Hastalarda Sağkalıma Etkisinin Araştırılması

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Abstract

Aim: Pathogenesis of cancer cachexia is not fully understood yet; however, adipocytokines are considered necessary in this context. We aimed to evaluate role of serum adiponectin, leptin, visfatin, resistin, C-peptide, IL-10 and IL-2 levels in the pathogenesis of cancer cachexia and to find out whether they are predictors of cachexia and to reveal their correlation with survival.

Material and Method: Fifty-three patients (34 males) and 20 healthy subjects as the control group were included in this study. Blood samples were stored in a deep freezer at -70°C and all samples were analyzed with an appropriate biochemistry kit. Along with demographic data and laboratory test results, serum adiponectin, leptin, IL-10, IL-22, C peptide, resistin, and visfatin levels were measured at 3 different times in both inpatient and control groups.

Results: There was no statistically significant relationship between adipocytokine levels and progression-free survival. Higher resistin and IL-10 levels were associated with shorter overall survival (p=0.035, p=0.14, respectively). There was no significant relationship between other cytokines and overall survival. Multivariate analysis has shown that higher serum Ca 19.9 levels (OR 0.226, P=0.005), lower BMI (OR 5.726, p= 0.007), higher serum IL-10 levels (OR 0.329, p= 0.042) were factors showing an impact on progression-free survival; lower serum albumin levels (OR 0.282, p=0.013), higher serum LDH levels (OR 0,338, p=0.012), low BMI at diagnosis (OR 5.19, p<0.0005) were factors having an impact on overall survival.

Conclusions: In our study, a correlation was found between resistin, adipocytokine, and IL-10 levels and overall survival.

Keywords: Cancer cachexia, adipocytokines, adiponectin, gastric cancer, colon cancer

Öz

Amaç: Kanser kaşeksisinin patogenezi henüz tam olarak anlaşılamamıştır; ancak adipositokinlerin bu bağlamda önemli olduğu düşünülmektedir. Serum adiponektin, leptin, visfatin, resistin, C-peptid, IL-10 ve IL-2 düzeylerinin kanser kaşeksisinin patogenezindeki rolünü değerlendirmeyi ve kaşeksinin belirleyicileri olup olmadıklarını ve sağkalım ile korelasyonlarını ortaya çıkarmayı amaçladık.

Gereç ve Yöntem: Elli üç hasta (34 erkek) ve kontrol grubu olarak 20 sağlıklı kişi bu çalışmaya dahil edildi. Kan örnekleri -70°C'de derin dondurucuda saklanmış ve tüm örnekler uygun biyokimya kiti ile analiz edilmiştir. Demografik veriler ve laboratuvar test sonuçları ile birlikte serum adiponektin, leptin, IL-10, IL-22, C peptid, resistin ve visfatin seviyeleri hem yatan hasta hem de kontrol grubunda 3 farklı zamanda ölçüldü.

Bulgular: Adipositokin düzeyleri ile progresyonsuz sağkalım arasında istatistiksel olarak anlamlı bir ilişki yoktu. Daha yüksek resistin ve IL-10 seviyeleri, daha kısa genel sağkalım ile ilişkilendirildi (sırasıyla p=0.035, p=0.14). Diğer sitokinler ile genel sağkalım arasında anlamlı bir ilişki yoktu. Çok değişkenli analiz, daha yüksek serum Ca 19.9 düzeylerinin (OR 0.226, P=0.005), daha düşük BMI (OR 5.726, p= 0.007), daha yüksek serum IL-10 düzeylerinin (OR 0.329, p= 0.042) progresyonsuz sağkalıma etki gösteren faktörler olduğunu göstermiştir. Daha düşük serum albümin seviyeleri (OR 0.282, p=0.013), daha yüksek serum LDH seviyeleri (OR 0.338, p=0.012), tanı anında düşük BMI (OR 5.19, P<0.0005) genel sağkalımı etkileyen faktörlerdi.

Sonuç: Çalışmamızda, resistin, adipositokin ve IL-10 düzeyi ile genel sağkalım arasında bir ilişki saptandı.

Anahtar Kelimeler: Kanser kaşeksisi, adipositokinler, adiponektin, mide kanseri, kolon kanseri

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INTRODUCTION

Cachexia is defined as a complex process including a multitude of factors such as adipose tissue loss due to lipolysis, loss of striated muscle, increase in energy expenditure during rest, and decrease in food intake.[1,2] Nowadays cachexia is used to define severe weight loss due to starvation or disease; however, it also points out a body mass index (BMI) < 18.5 kg/m^2. Recently, > 6% weight loss during the last 6 months along with hypercatabolic state during life-threatening conditions such as cancer are described as cachexia.[1-3] Cancer cachexia is a multifactorial syndrome occurring because of a lack of food intake in which various metabolic abnormalities, including hypermetabolism. There is an active catabolic process developing because of systemic inflammation involving multiple mediators including proinflammatory cytokines, neuroendocrine hormones, or factors inherent to the tumor itself.[4]

Cancer Cachexia is Evaluated Mainly in Two Groups

Primary cachexia: It is the result of metabolic alterations. Systemic inflammatory response is triggered and released biochemical substances (cytokines such as TNF-α, IL-1, IFN-γ, IL-6) increase metabolic rate and suppress appetite very early and lead to early satiety. As a result of metabolic abnormalities anorexia develops and loss of muscle and adipose mass ensues anorexia.[5] Based on data from some patients with cancer, it is suggested that there may be correlation between increased cytokine levels and progression of cancer.[6] Along with inflammatory process several biochemical hormones (visfatin, leptin, resistin) are released. As a result of this inflammatory process loss of adipose tissue and muscle mass occur.[7]

Secondary cachexia: Occurs because of factors impeding the intake of food. Mechanic obstruction due to tumor, taste, and odor abnormalities due to chemotherapy, diarrhea or constipation, fatigue, mucositis, nausea, vomiting, and pain are the most common accompanying symptoms and signs.[5] There is another term in the literature tertiary cachexia. It emerged after the detection of some findings that pointed out the impact of psychosocial factors on dietary intake in advanced-stage cancer patients.[7,8]

It's considered that the relationship between the tumor and the host contributes to the development of cachexia. Both experimental and clinical observations have revealed the presence of two types of catabolic factors. The first type is tumor-derived cachexia (proteolysis forming factor and lipid-mobilizing factor) and the other type is proinflammatory cytokines associated with the host (IL-1, IL-6, TNF- α, interferon-γ, cachexin, etc.). Furthermore, the imbalance between proinflammatory and anti-inflammatory cytokines is also suggested as a contributor to cachexia.[9] In recent years, importance of adipose tissue is emphasized in studies on cancer cachexia.[10]

Adiponectin, leptin, resistin is visfatin are among the adipokines exerting significant effects on lipid metabolism. Leptin suppresses food intake and stimulates energy consumption. Adiponectin and resistin are associated with body mass index and insulin resistance.[10] Visfatin stimulates angiogenesis by increasing endothelial proliferation. This was found to be associated with cancer development and cardiovascular diseases.[11] Higher concentrations of C-peptide are found to be directly related to cancer risk in some studies.[12,14] IL-10 is an anti-inflammatory cytokine and suppresses inflammatory process. In chronic gastritis excessive production of IL-10 allele may lead to helicobacter pylori colonization and mucosal inflammation.[15] IL-22 is a more recently described cytokine relative to others and it's suggested as a marker for GIS cancer screening and a target for treatment in the future.[16] Relationship between systemic inflammation and cancer and cachexia syndrome is not fully understood yet. However, now it's accepted that adipokines and proinflammatory cytokines have significant roles in these clinical pictures. One of the cancers leading to cachexia in the advanced stages is gastrointestinal system (GIS) cancer.[17] In this study, we aimed to evaluate role of serum adiponectin, leptin, visfatin, resistin, C-peptide, IL-10 and IL-22 levels in the pathogenesis of cancer cachexia and to find out whether they are predictors of cachexia and to reveal their correlation with survival.

MATERIAL AND METHOD

Pamukkale University Medical Faculty Medical Ethics Board approved our study with approval number 12.10.2010.06 and 53 consecutive chemotherapy-naive patients who have referred to our hospital and pathologically diagnosed as having gastric, colon, and rectum carcinoma were evaluated. The patients in advanced stages (stage III and IV) of the disease with ECOG performance status 0, 1, and 2 were included. The patients with performance status 3 or worse during the referral, patients in earlier stages of the disease, and who haven't signed written informed consent were excluded from the study. A control group consisting of 20 healthy individuals and not using any medication was established. The age and sex of the individuals in the control group were matching with the patient group. Weight loss during the time of diagnosis was described as weight loss >10% in the last 6 months ad cachexia was described as BMI ≤18.5. The individuals within both groups were interviewed about the object and scope of the study and written informed consent from patients was obtained.

Biochemical Analysis

From the advanced-stage gastrointestinal system (gastric and colorectal) cancer patients referring to Pamukkale University Medical Faculty Medical Oncology Department for treatment and from the control group consisting of healthy volunteers 15 ml venous blood samples were obtained to vacuumed plain tubes after at least 8-12 hours of overnight fasting at 08:00-09:00 hours before treatment and at 3rd and 6th months after treatment and the blood was centrifuged at 15000 rpm for 15 minutes to separate serum and it was stored at -70 °C in the deep freeze and the tests were done by using all of the samples with appropriate biochemical kits.

Measurements (Human adiponectin, leptin, IL-10, IL-22, C peptide, resistin, visfatin-Firm: Boster Immunoleader Ltd.) were done by ELISA (Enzyme-Linked Immunosorbent Assay) method (Digital and analog system, DAS, Plombara Sabina Italy). Adiponectin, leptin, visfatin, resistin, C-peptide IL-10, and IL-22 cut-of values were calculated. The values were 3.6258 ng/ml for Adiponectin, 2319,5459 pg/ml for leptin, 11.0442 pg/ml for resistin, 7350.5334 pg/ml for visfatin, 9.4532 ng/ml for C-peptide, 157,7016 pg/ml for IL-10, 116.1121 pg/ml for IL-22. Values equal to or lower than these figures were considered low and higher levels were considered high. Demographic characteristics of patients, type of tumor, and previous chemotherapies were recorded by using data from the patient charts. From the obtained blood samples hemogram was performed by using CELL-DYN 3700 Systems and CELL-DYN Sapphire instrument and albumin, CRP, Lactate dehydrogenase (LDH), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (AST), glucose was measured by Roche/Hitachi Cobas c Systems, Cobas c 501 and Roche/Hitachi Cobas c Systems, e 601 Module instrument.

Anthropometric Measurements

Height, weight, waist and hip circumference, arm circumference, and triceps thickness of the patients and control group were measured before treatment and at the time of referral. Height and weight measurements were done on a calibrated scale with a height gauge by the same person while the subjects were in a fasting condition. Body mass index (BMI) was calculated by this formula: weight (kg)/height^2(m^2). 18.5-24.9 kg/m^2 was considered normal and >25 kg/m^2 was considered overweight and obese.[18] For waist circumference measurements benchmarks were the narrowest diameter between arcus costarium and spina iliaca anterior posterior (superior); for hip circumference the highest diameter traversing gluteus maxiumus in the back and symphysis pubis at the front and the measurement was done by a tape measure. Waist/hip ratio was calculated (normal values were < 0.95 for males and < 0.8 for females).[18] Arm circumference was measured from the midpoint of the distance between olecranon and acromion. <18 cm and <20 cm was considered pathological respectively for females and males.[19] Triceps thickness was measured to evaluate thickness of subcutaneous adipose tissue and the measurement was done by using a caliper which is a special device from the midpoint of the distance between olecranon and acromion 3 times and average of these measurements was recorded. Values <10 mm and <13 mm were considered as lack of nutrition respectively for males and females.[19]

Statistical Analysis

Social Sciences version 22. 0 (SPSS-22.0, for windows) package program was used for statistical analysis. Descriptive statistics were as percentage for categorized variables and as mean for continuous variables. In dual comparisons Ki-square test was used for categorized variables and for continuous variables non-parametric tests Mann Whitney-U or Kruskal-Wallis were used because the distribution was non-normal and Freidman test was used in case there is repeated analysis. In dual comparisons of survival analysis Kaplan Meier method was used and statistical differences were evaluated by log rank test. The highest sensitivity and specificity values of cut-off values were selected by using SPSS 22.00 version roc-curve analysis.

RESULTS

A total of 53 (34 male, 64.2%) patients with advanced stage grade (III and IV) colorectal or gastric cancer were included. Main clinical and demographic characteristics are shown in **Table 1**. 16 males (80%) and 4 females (20%) were selected as a control group. The mean age was 63.1±6.3 years. They had no comorbidities, and their performance was good (ECOG PS 0). In the control group cachexia, anemia, leukocytosis, high CRP or LDH level and low albumin level haven't been observed and in fifteen subjects (75%) BMI was > 25 kg/m^2 and none of them had a history of tobacco or alcohol use.

Table 1 Demographic and clinical characteristics of the patients (before treatment)

Characteristics	Median-year, (range)
Age	63.32 (39 -79)
Characteristics	n(%)
Gender	
Male	19 (35.8)
Female	34 (64.2)
Organ involvement	
Stomach	25 (47.16)
Colon	25 (47.16)
Rectum	3 (5.66)
Stage	
III (three)	21 (39.62%)
IV (for)	32 (60.37%)
Tobacco use (yes/no)	28/25 (52.8/ 47.2)
Use of Alcohol	46/7(86.8/ 13.2)
Performance status(0/1) 2	44 (83) /9 (17)
Comordity (yes/no)	25/28 (47.2/ 52.8)
Weigt loss during (yes/no)	48/5(90.6/ 9.4)
Family history of cancer (yes/no)	11/42 (11.32/ 88.68)

*p < 0.05 is considered as significant. SD: standart deviation

Age, gender, anthropometric measurements, biochemical test values, serum adiponectin, leptin, resistin, visfatin, C peptide, and IL-22 values were compared between groups (**Table 2**). As it's shown in **Table 2** resistin levels were higher in the patient cohort compared to the control group and the increase was statistically significant (p<0.001). Adiponectin and visfatin levels were lower in the patient cohort and the difference was statistically significant for both parameters (p=0.002, p=0.001). There was no statistically significant difference between the groups in terms of Leptin, C-peptide, IL-10, and IL-22 values. In **Table 3** prospective cachexia-associated biomarker follow-up results of the patient group were measured at 3 different times. There was no statistically significant difference in the prospective cachexia-associated biomarker follow up results of patient group measured in 3 different time except serum C-peptide value (p=0.002).

Table 2 Characteristics of patient and control group (mean±SD).

	Patient	Control	P
Age (year)	63.3±10.4	63.1±6.2	0.484
Sex (female/male)	19(35.8)/34(64.2)	4(20)/16(80)	0.263
Height(cm)	162.84±8.95	171.1±6.75	0.001*
Weight (kg)	64.58±12.27	80.6±10.8	<0.001*
BMI (kg/m^2)	26.49±3.66	27.2±2.9	0.002*
Waist circumference (cm)	86.28±14.38	98.2±7.6	0.001*
Hip circumference (cm)	93.96±14.87	104.2±5.4	<0.001*
Triceps thickness (mm)	1.79±0.62	3.6±0.5	<0.001*
Arm circumference (cm)	23.6±4.92	32.2±2.2	<0.001*
Hemoglobin (gr/dl)	12.53±1.89	14.5±1.0	<0.001*
WBC (K/µL)	8632±3523.6	7503.5±335.7	0.407
Neutrophils (K/µL)	5888.8±2899.3	4112.5±272.7	0.009*
PLT (K/µL)	314018.8±1.19	249050±8938.2	0.011*
Albumin (g/dl)	3.73±0.72	4.4±0.3	<0.001*
CRP (mg/dl)	3.53±5.22	0.3±0.1	<0.001*
Glucose (mg/dl)	116.53±45.55	95.0±4.9	0.021*
LDH (U/L)	374.96±708.02	194.1±7.1	0.209
IL-10 (ng/ml)	202.89±148.27	201.46±230.42	0.350
IL-22 (ng/ml)	185.89±153.62	215.83±96.04	0.070
C peptid (ng/ml)	8.23±2.02	8.66±1.58	0.496
Adiponectin (ng/ml)	5.18±3.89	8.01±3.87	0.002*
Leptin (ng/ml)	2.254±4460	2.39±3.7	0.990
Resistin (ng/ml)	7365.39±215.77	7125.06±352.91	<0.001*
Visfatin (ng/ml)	12.18±28.22	16.88±17.52	0.001*

*p < 0.05 is considered as significant. SD: standart deviation
**BMI: body mass index; WBC: White Blood Cell, PLT: platelets; CRP: c-reactive protein; LDH: Lactate dehydrogenase

During the median 8 months of follow-up (range 6-21 months) the disease has progressed in 16 of the 53 patients (30.18%). Progression-free survival was assessed and there was no statistically significant difference between those with high and low levels of leptin, adiponectin, resistin, C peptide, IL-22, and visfatin (p=0.711, p=0.568, p=0.774, p=0.997, p=0.405, 0.390, respectively) regarding progression. In patients with higher IL-10 levels progression-free survival was 36.64 weeks and in those with lower levels, it was 52.88 weeks (p=0.023). As it's shown in **Table 4** after Cox regression analysis 3 of the 5 parameters within the model were found to be statistically higher.

Table 4. Multivariate analysis results of progression free survival

Multivariate analysis results of progression free survival */**			
	OR	95%CI max-min	P
CA-19-9	0.226	0.080-0.639	0.005**
BMI	5.726	1.598-20.514	0.007**
IL-10	0.329	0.110-0.960	0.042**
Pathology			
Adenocarsinoma	0.389	0.035-4.375	0.614
Signet ring cell	0.798	0.049-13.091	0.953
Undifferentiated	4.599	0.171-123.909	0.144
Hemoglobin	0.276	8.6-13.2	0.20

Cox regression analysis was done and 5 parameters were evaluated in the model and 3 parameters was found to be significant.**p < 0.05 is considred significant. SD: standart deviation, OR:odds ratio BMI: body mass index

In patients with high levels of leptin, adiponectin, C peptide, IL-22, and visfatin mean overall survival wasn't significantly different from those with low levels (p=0.787, p=0.702, p=0.224, p=0.954, p=0.205). As it's shown in **Figure 1**, the mean overall survival was 9 months in patients with a high level of IL-10 and 14 months in patients with low levels of IL-10. The difference was statistically significant (p=0.014). As it's shown in **Figure 2**, the mean overall survival was 9 months in patients with a high level of resistin and 14 months in patients with a low level of resistin. The difference was statistically significant (p=0.035). In Cox regression analysis, hypoalbuminemia, high LDH level, and presence of low BMI at the time of diagnosis caused statistically significant overall survival differences (**Table 5** and **6**).

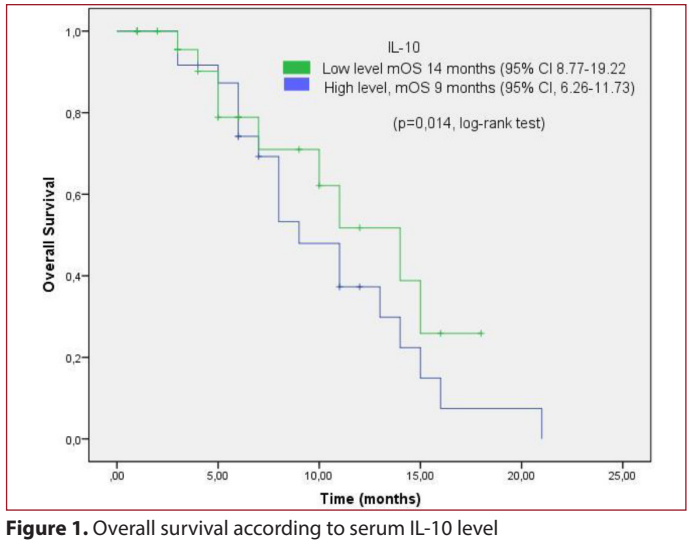

Figure 1. Overall survival according to serum IL-10 level

Table 3 Prospective cachexia-associated biomarkers follow up results of patient group measured in 3 different time period (mean±SD).

(ng/ml)	Before treatment		3rd month		6th month		P
	n	mean±SD	n	mean±SD	n	mean±SD	
IL-10	54	202.89±148.27	37	202.5±172.88	14	204.58±250.02	0.526
IL-22	54	185.89±153.62	37	130.68±345.56	14	208.18±530.69	0.238
C peptide	54	8.23±2.02	37	10.8±0.95	14	9.09±1.93	0.002*
Adiponectin	54	5.18±3.89	37	2.50±1.57	14	4.1±3.02	0.135
Leptin	54	2.254±4460	37	1812.3±694.9	14	1976.1±519.8	0.138
Resistin	54	7365.39±215.77	37	7249.6±443.3	14	7200.2±377.1	0.751
Visfatin	54	12.18±28.22	37	21.6±42.87	14	18.96±27.12	0.424

*p < 0.05 is considered as significant. SD: standart deviation

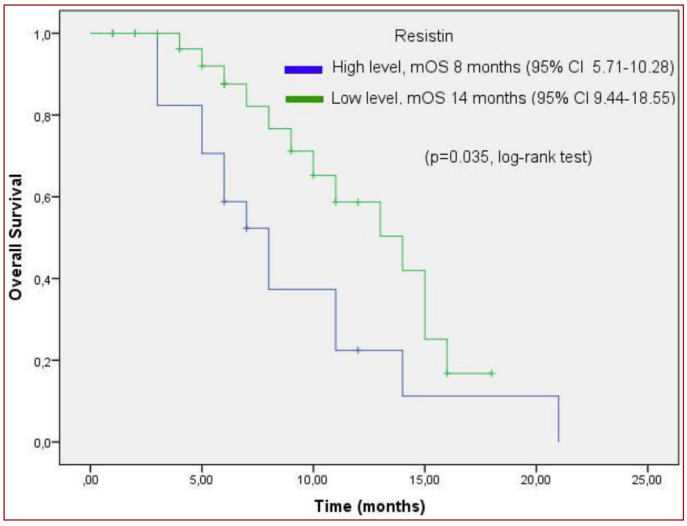

Figure 2. Overall survival according to serum resistin level

Table 5. Multivariate analysis results in overall survival -1

Multivariate analysis results of overall survival -1 */**			
Variable	**OR**	**95%CI max-min**	**P**
Hypoalbuminemia	0.282	0.104-0.764	0.013**
LDH	0.338	0.146-0.786	0.012**
Anemia	0.470	0.200-1.102	0.083
CRP	0.676	0.116-3.949	0.664
Leucocytosis	0.736	0.325-1.666	0.462
CEA	0.944	0.360-2.475	0.906

* Overall survival multivariate analysis performed by Cox regression analysis and 6 parameters were evaluated in the model and 2 parameters was found to be significant.**p < 0.05 is considred significant. SD: standart deviation
** CRP: c-reactive protein; LDH: Lactate dehydrogenase

Table 6. Multivariate analysis results of overall survival-2

Multivariate analyssi results in overall -2*/**			
Variable	**OR**	**9 5%CI max-min**	**P**
BMI during diagnosis	5.19	2.093-12.867	<0.005**
LDH	0.257	0.087-0.761	0.014**
IL-10	0.585	0.233-1.470	0.254

* Overall survival multivariate analysis performed by Cox regression analysis and 3 parameters were evaluated in the model and 2 parameters was found to be significant. **p < 0.05 is considred significant. SD: standart deviation

DISCUSSION

Gastrointestinal system cancers are the third leading cause of cancer deaths after lung cancer in males and lung and breast cancer in females.[20] Prevalence of malnutrition in gastrointestinal system cancer patients is 42-87%.[21-23] In cancer patients, weight loss was found to be correlated with lower survival and decrease in life quality.[24,25] Patients with weight loss comprised 90.5 % of our patient cohort. In anthropometric measurements, height, weight, BMI, waist circumference, hip circumference, triceps thickness, arm circumference was lower in patient's cohort compared to control group and the difference was statistically significant. Moreover, in the patients with weight loss at the time of diagnosis waist circumference, hip circumference, weight, BMI were lower. In our study, it was observed that weight loss at the time of diagnosis had an impact on progression and survival.

In the subcutaneous adipose tissue leptin production is more than in visceral adipose tissue and has the best positive correlation with body mass index and body fat ratio.[26] In a study regarding leptin levels and including 39 patient's leptin level was found to be statistically significantly lower in cachectic GIS cancer patients and low level of leptin was found to be associated both with loss of adipose cells and increase in inflammatory cytokines.[26] Levels were low in gastrointestinal and pancreatic cancer patients, but high in breast and gynecological cancers.[27,28] It was reported that there is a tendency for lower survival in patients with weight loss and poor performance though there was no correlation between these parameters and time to progression of the disease.[29] In our study prospective leptin follow up results of patient group measured in 3 different time period revealed no significant finding (p=0.138). In a study by Nakajima et al.[30] leptin levels of gastric cancer patients and healthy controls were compared. According to the results of this study leptin levels progressively decreased as the stage of the disease progressed.[30] In our study, the mean progression-free survival was 46. 05 weeks in patients with high levels of leptin and 46.18 weeks in patients with low levels of leptin (p=0.711). Mean overall survival was 44.76 weeks in patients with high levels of leptin and 43.81 weeks in patients with low levels of leptin; however, the difference wasn't statistically significant. Adiponectin is a protein released from adipose tissue. The physiological role of adiponectin is not fully elucidated yet; however, there are some studies pointing out its antiatherogenic and anti-inflammatory effects on endothelial cells and macrophages and showing a decrease in adiponectin levels in the presence of hypertension, diabetes, and metabolic syndrome.[31,32] In a study carried out on breast and colon cancer patients; advanced age and female sex were found to be correlated with high adiponectin levels.[33] Adiponectin blocks the effects of TNF-α. Lower adiponectin level increases the effect of TNF-α on tumor cell proliferation and thus promotes carcinogenesis. In our study, in the adiponectin patient group adiponectin was lower compared to the control group. Proinflammatory and growth-stimulating effects of adiponectin on colonic epithelial cancer cells were detected. In a prospective study, plasma adiponectin level was conversely related to colorectal cancer risk in males. This correlation was found to be independent of BMI; waist circumference, waist: hip ratio, and physical activity.

It has been suggested that resistin is a mediator of metabolism including particularly glucose metabolism, a regulator in adipogenesis and a modulator in inflammation.[35] In a study conducted on 30 health volunteers and 60 gastric cancer patients there was no direct relationship between resistin level and cancer cachexia. Effects of resistin in cancer cachexia are due to insulin resistance and ineffective use of blood glucose. Resistin level was found to be higher in cachectic patients relative to non-cachectic patients and healthy volunteers.[36] In our study, resistin was higher in the patient group compared

to the control group (p<0.001). Moreover, it was found that resistin levels were higher in patients with weight loss at the time of diagnosis but there was no difference in patients and control group subjects without weight loss. Higher resistin levels in patients with weight loss at the time of diagnosis support the notion that resistin may be involved in this hypercatabolic process. In a case-control study conducted on colorectal cancer patients, Nakajima et al. stated that resistin and visfatin each may be a good biomarker in predicting potential colorectal malignancy and stage progression in colorectal cancer independent from BMI.[37] Overall survival was worse in patients with high resistin level compared to patients with low resistin level. The difference was statistically significant (8 months vs 14 months, p=0.035). Our study has shown that resistin is involved in cancer and cachexia as a proinflammatory cytokine and although it can't be used as a diagnostic or prognostic marker yet there is still a need for further studies on this substance.

C peptide is secreted in equal amounts with insulin after insulin biosynthesis and thus may be used as an endogenous insulin secretion marker; however, its cellular effects aren't fully elucidated, yet.[30] It's known that components of metabolic syndrome increase cancer risk. In our study, C peptide levels were higher in the control group compared to patient group, but the difference wasn't statistically significant. In the group with weight loss C peptide level was higher but difference wasn't statistically significant (p=0.260). In a study by Nakajima et al.[30] C peptide levels of gastric cancer patients were compared with healthy controls. There was no correlation between BMI and C-peptide level. According to the results of the same study, in parallel to progression of the disease stage BMI and C peptide levels have progressively decreased.[30] On the other hand, in our study, C Peptide level was 8.23ng/dl in the 1st measurement, 10.8 ng/dl in the 2nd measurement and 9.09 ng/dl in the 3rd measurement. Serum C peptide level which was lower than cut off value at the time of diagnosis was found to be higher than cut off value in the 2nd and 3rd measurements. The difference was statistically significant (p=0.002). In patients with higher C peptide level median progression free and overall survival was longer but the difference wasn't significant (p=0.097, p= 0.224). Intracellular signaling pathways of C peptide is not fully known and cellular mechanism links are clinically important for components of metabolic syndrome and carcinogenesis. We assume that furthermore comprehensive studies about C peptide and gastrointestinal cancers are needed.

Even though cancer cachexia couldn't have been fully elucidated, currently some important key mediators are discovered. IL-1, IL-6, IL-10, TNF-α, IFN-g are the mediators with a proven role in cancer cachexia pathogenesis.[38] It's assumed that IL-10 induces increase in cell proliferation, and this leads to decrease in apoptosis and thus promotes tumor growth. IL-10 production and release are conducted by immune cells along with cancer cells. Shibata et al. have studied serum IL-10 and IL-12 levels in colorectal cancer patients. IL-10 levels were higher in cachectic patients compared to healthy control group. In the same study, IL- 10 levels were lower in early-stage colorectal cancer.[39] In a study by Stanilov et al.[40] increasing IL-10 levels were reported to be related with progression in colorectal carcinoma. De Vita et al.[41] compared IL-10 levels measured before and after chemotherapy in advanced stage gastrointestinal system cancer patients. The levels were lower in those responding to chemotherapy than nonresponding patients. This study led to the premise that IL-10 levels measured before treatment may be helpful in detecting the disease regardless from progression. In the same study, IL-10 levels were higher in the carcinoma patients compared to control group.[41] Similarly, also in our study IL-10 level was higher in stage 4 diseases compared to stage 3; however, there was no statistically significant result between patient group and the control group (p=0.350).

In carcinogenesis role of immune response of the host, cytokines, immune mediators, and associated inflammation have been increasingly proven. IL-22 is a member of IL-10 and derived from T cells and it's responsible from epithelial immunity and mucosa tissue repair.[42] Thomson et al.[16] reported that IL-22 gene variation (rs1179251 SNP) is related with risk of colon cancer. In our study IL-22 level was lower in the patient group compared to control group (p=0.07). Furthermore, mean progression free survival was 45.64 weeks in patients with high IL-22 levels and 41.84 weeks in those with low levels and mean overall survival was 45.58 weeks in patients with high IL-22 levels and 46.06 weeks in those with low levels; however, differences weren't statistically significant (p= 0.405, p= 0.954).

Visfatin which is also known as Pre-B cell colony-enhancing factor (PBEF) is a recently described novel adipokine secreted from visceral adipose tissue.[43] It's biological function and its role within the mechanism as a cytokine couldn't be fully elucidated yet. It's presumed that by inhibiting visfatin activity treating cancer or an increase in sensitivity to chemotherapy may be possible.[43] In acute and chronic inflammation serum visfatin levels increased. During inflammation process its production increases and this leads to an increase in secretion of cytokines such as tumor necrosis factor -α (TNF-α), IL–1, IL–6, IL–10.[44] Nakajima et al.[30] reported that visfatin within the serum obtained from patients with colorectal or gastric cancers may be related with the stage and progression of the disease. Additionally, they suggested that visfatin may be a very good biological marker for potential malignancy and progression in colorectal adenocarcinoma. In our study we did noy detect any effect of visfatin levels on progression and mean progression free survival. Overall survivals were longer in patients with high visfatin levels compared to those with low levels, however, the results weren't significant (p=0.39, p=0.205). Detection of visfatin also in inflammatory cells and elevation in plasma levels during various inflammatory diseases implies that different cytokines may be effective in visfatin synthesis and secretion.

CONCLUSION

In this study, 53 advanced stage gastrointestinal system cancer patients and 20 healthy control group subjects were evaluated regarding their clinical and laboratory data. In the patient group BMI, weight, waist circumference, hip circumference, arm circumference, triceps thickness, hemoglobin, albumin, adiponectin, visfatin leptin, C-peptide and IL-22 levels were low; neutrophils, platelets, CRP, glucose, resistin WBC, LDH and IL-10 levels were high. Furthermore, a relationship between resistin which is a type of adipokine, and IL-10 level were detected. Our results were broadly in line with the literature. There is scarce amount of study in the literature about this issue. In our study, relatively low number of the patient cohort may prevent data which are statistically more significant to be obtained. We assume that, for a final decision accumulation of more literature is needed and studies with higher number of patients should be conducted.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ethical Committee of Pamukkale University, Scientific Research Projects Commision dated 07/03/2013 and numbered 01, numbered 2011TPF009.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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