SERUM LEVELS OF OMENTIN-1 IN PATIENTS WITH ADVANCED EPITHELIAL OVARIAN CANCER: THE IZMIR ONCOLOGY GROUP (IZOG) STUDY

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ABSTRACT

Background*: The role of molecular markers in ovarian cancer is still a matter of debate. This study was conducted to determine the clinical significance of serum Omentin-1 in epithelial ovarian cancer (EOC) patients in the current matched case-control study.*

Material and methods*: Fourty-one patients with advanced EOC and 41 healthy people were included in the study. Serum Omentin values were measured by quantitative ELISA method.*

Results*: The median serum Omentin-1 values was 46.6 pg/ml in patients and this was significantly higher than healthy controls (median 35.5) (p=0.045). There was positive correlation between serum omentin and serum CA-125 levels (r = 0.34, p =0.028). We found no relationship between serum Omentin-1 levels and any prognostic parameters analyzed, including age of the patients, histology, tumor grade, stage of the disease, debulking surgery and response to chemotherapy. Survival analysis did not show statistically significant effect of serum Omentin-1 level on overall survival (p = 0.91)*

Conclusions*: These results indicated that serum Omentin-1 values were significantly elevated in patients with advanced ovarian carcinoma compared to healthy people. Further studies with a greater number of patients are required to confirm the importance of serum Omentin-1 levels in ovarian cancer.*

Keywords*: Serum Omentin-1, advanced stage, Overall survival, Ovarian Cancer.*

DOI: 10.19193/0393-6384_2017_4_080

Received *November 30, 2016;* ***Accepted*** *March 20, 2017*

Introduction

Ovarian cancer is one of the most aggressive gynaecological malignancies and most often the high mortality is due to the lack of a screening strategy for early detection.

Adipose tissue is recognized as an active endocrine organ that produces a number of endocrine substances referred to as "adipokines" like omentin-1[(1)]. Omentin, also known as 'intelectin' a 38-40 kDa protein that is primarily secreted by visceral adipose tissue, is also expressed in endothelial cells, thymus, small intestine, colon, lungs and ovary[(1,2)]. Adipose tissue can induce a state of low-grade inflammation due to secretion of proinflammatory adipokines and the reduced secretion of anti-inflammatory ones[(3)].

In recent years, many adipokines has been investigated as an prognostic or predictif marker in oncology.

Pathogenesis of ovarian cancer is related various tumorogenetic pathways including Akt signal-

ing. Akt plays a crucial role in glucose metabolism, cell cycle and transcriptional regulation, apoptosis, and tumor progression[4]. Akt signalling has been shown to play a role in angiogenesis and tumorogenesis[5,6]. Previous studies have evaluated omentin-1 in policystic ovarian syndrome and documented its enhancing capacity in AKT phosphorylation / activation[7]. Thus, omentin has been thought to be a facilitator of carcinogenesis and has studied in colorectal cancer, renal cell cancer, prostate cancer and hepatocellular carcinoma[8,9,10,11].

Previous studies on the association of EOC and adipokines (e.g., leptin and adiponectin) have reported conflicting results. However, the biological role of omentin in carcinogenesis is not fully understood. To our knowledge, the serum omentin level has not been studied in patients with EOC. Therefore, the objective of this study was to evaluate the serum omentin-1 in EOC and its relationship with other factors.

Methods

Patients and controls

Fourty-one patients with advanced epithelial ovarian carcinoma, pathologically verified, consecutively admitted to the Department of Medical Oncology,Izmir Katip Celebi University, Ataturk Training and Research Hospital from January 2014 to October 2015 were investigated. Median ages were 57 years (range: 38-80) for ovarian cancer patients and 55 years (range: 46-73) for healthy control. Serum samples were obtained from advanced stage patients before treatment. Staging was performed on FIGO (International Federation of Gynecology and Obstetrics) classification by radiologic and pathologic basal results. Histological type and grade were classified according to the World Health Organization (WHO) criteria. Residual tumor mass was assessed using the clinical classification of≤ 1 or >1 cm, which was standard at the time of surgery.Detailed clinical patient data are shown in Table 1.

All patients received the following chemotherapy regimen as first line of treatment: paclitaxel at a dose of 175 mg/m2 and carboplatin that was dosed according to the Calvert formula for the desired area under the curve of 5 on day 1 of a 3-week cycle, for 6-8 courses. At the end of the complete treatment program, serum CA125 level evaluation and clinical and gynecological examination were performed every 3 months for the first 2 years, every 6 months for the next 3 years and every year thereafter. Patients underwent instrumental evaluation according to clinical status and CA125 level.

The control group consisted of 41healthy women with no previous history of malignancy or gynecologic disease. Blood samples from the patients and controls were into dry tubes and sera separated from cellular elements by centrifugation (at 1000 g for 10 min) within half an hour after blood sampling and all plasma samples were stored at -20°C until analysis. All of the samples were collected under the approval of the institutional review board and with adequate informed consents.

Measurement of serum Omentin levels

Serum omentin was measured with a sandwich enzyme immunoassay technique (CSB-E09745h,Cusabio,Wuhan,CHINA). Serum samples are pipetted into the microwells precoated with antibody specific for human Omentin. According to the assay principle the antibody captures the antigen present in the solutions during the incubation period. After removing any unbound substances, a biotin-conjugated antibody specific for Omentin is added to the wells. Following the wash period, avidin conjugated Horseradish Peroxidase is added. When the second wash period is finished, a substrate solution is added and color developed in proportion to the amount of Omentin. The color development is stopped and the intensity of the color is measured at 450nm.The detection range of the assay was 1.56-100 pg/ml. The inter - and intra assay coefficients of variation were <10% and <8%, respectively.

Statistical analysis

SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL., USA) was employed for data analysis. The established prognostic clinical factors such as age, FIGO stage, nuclear grade, debalking status, tumor histology, operation timing, serum Omentin ve Ca125 levels were coded as binary variables (age: ≤ 55 versus >50 years; FIGO stage: IIIC versus IV; debalking status: optimal versus suboptimal, tumor histology: serous versus non-serous; grade: gr1-2 versus gr 3; operation timing: primary debulking surgery versus interval debulking surgery after neoadjuvant chemotherapy, Omentin-1 level low (≤median) versus high (> median). To meet the nonnormal distribution of serum Omentin-1levels, nonparametric tests were used for statistical analysis. The serum levels among the subgroups were

analyzed with the Mann- Whitney U tests. Survival analysis and curves were established according to the Kaplan-Meier method and compared by the log-rank test. OS was defined as the time from diagnosis to the last follow-up or death. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All statistical tests were carried out two-sided and a P value ≤0.05 was considered statistically significant.

Results

Patient characteristics

Patients characteristics are reported in Table 1. The median age was 57 years. Twenty-nine (70.7%) had the International Federation of Gynecology and Obstetrics (FIGO) stage IIIC. The histologic distribution was as follows: 35 serous, 1 clear cell, 1 mucinous,2 mixed tumors, and 2 endometrioid. Initial histologic grade was 1 well differentiated (2.4%), 3 moderately differentiated (7.4%), and 37 poorly differentiated (90.2%). Following surgical debulking, residual disease by size was distributed as follows: 28 (68.3%) with <1 cm and 12 (29.3%) with >1 cm.During the following period, 15(%36.6)patients died.

Serum levels of Omentin-1 in patients and controls

The median serum levels of Omentin-1 in patients with ovarian cancer and controls are presented in Figure 1. A total of 82 cases were included in the study: 41 of them were patients with advanced overian cancer and the other 41 cases were a woman healthy control group. The median serum Omentin-1 values was 46.6 pg/ml in patients and this was significantly higher than healthy controls (median 35.5) (p=0.045) (Table 2). However, there was no statistically significant differences between the groups in terms of body mass index (BMI)(30.7 for partients vs 29.0 for healties, p=0.6)

Prognostic Implications of Serum Omentin Levels in Ovarian Cancer

The relationship between serum median Omentin-1 levels and the clinicopathological findings are shown in Table 3.We found no relationship between serum Omentin-1 levels and any prognostic parameters analyzed, including age of the patients, histology, tumor grade, stage of the disease, debulking surgery and response to chemotherapy.

Characteristic	n (%)
Age (years), median(min-max)	57(38-80)
Histopathological findings	
Serous	35(85.4)
Endometrioid	2(4.9)
Clear cell	1(2.4)
Mucinous	1(2.4)
Mixed	2(4.9)
Clinical response to firt-line chemotherapy	
Yes	35(85.4)
No	6(14.8)
Platinum response	
Semi-sensitive (6-12 months)	11(26.8)
Sensitive (>12 months)	24(58.6)
Resistan (≤ 6months)	6(14.6)
Disease stage at initial diagnosis	
Ic	2(4.8)
IIIc	29(70.7)
IV	10(24.4)
Grade	
1	1(2.4)
2	3(7.4)
3	37(90.2)
Residual tumor size (cm)	
≤ 1.0 (optimal resection)	28(68.3)
>1.0 (suboptimal resection)	12 (29.3)
None	1(2.4)
Operation time	
PDS	31(77.5)
NACT-IDS	9 (22.5)
Disease status at last follow-up	
No Evidence of Disease (NED)	2(4.8)
Evidence of Disease (ED)	25(61.0)
Dead	14(34.2)
Initial serum CA-125 level	101 (5- 3092)
(U/ml median, range)	

Table 1: Clinical characteristics of patients with epithelial ovarian cancer.
PDS: Primary debulking surgery
NACT-IDS: Interval debulking surgery after neoadjuvant chemotherapy

In correlation analysis using pearson's correlation coefficient, there was significant positive correlation between serum Omentin-1 level and CA-125 (r = 0.34, p =0.028). Univariate analysis of Overall survival was performed by Kaplan-Meier method and log-rank test was performed for clinical findings; the cut-off values of each biomarker were calculated using these tests.

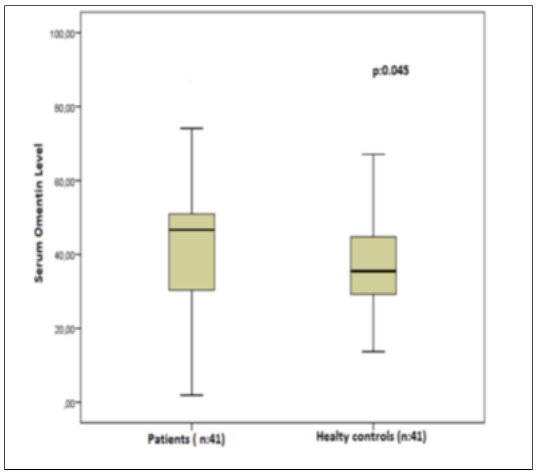

Figure 1: Serum Omentin levels in healthy controls and patients.

Serum levels	Patients (n= 41)	Controls (n= 41)	P value
Median Omentin (pg/ml)	46.6	35.5	**0.045**
Range	1.9-86.1	13.7-67.1	
Mean Omentin level±SD (pg/ml)	43.8±19.1	37.4±12.0	

Table 2: Serum Omentin levels in patients and controls.

The results of univariate analysis for OS are summarized in Table 4. Debulking status (p<0.001), platin sensitivity (p=0.007), response to initial chemotherapy (p<0.001) were significantly associated with survival. There is no effect on survival the level of serum Omentin-1(p = 0.91). Multivariate analysis was not performed because of the limited sample size and the low number of outcome events.

Discussion

In this study, serum Omentin-1 levels in patients with ovarian cancer were significantly higher than healthy women controls. However, There was no relationship between serum Omentin-1 levels and any prognostic parameters analyzed. Survival analysis did not show statistically significant effect of serum Omentin-1 concentration on overall survival.

This is the first study to evaluate serum Omentin-1 levels in patients with ovarian cancer.

Variables		Omentin [median (range, U/l)]	P value
Age (years)			
≤55	17	45.4 (1.9-86.0)	
>55	24	46.9(12.7-86.1)	0.27
Stage			
IIIC	29	46.7 (1.9-86.1)	
IV	10	46.1(17.2-62.3)	0.59
Tumor histology			
Serous	36	46.7 (1.9-86.0)	
Non-serous	5	46.3(12.7-86.1)	0.81
Debulking surgery			
Optimal	28	46.2 (1.9-86.1)	
Suboptimal	12	46.4 (11.9-65.1)	0.33
Grade			
Gr1-2	4	48.1(46.3-86.1)	
Gr3	37	45.6(1.9-86.0)	0.21
Platin sensitive			
Sensitive	24	45.9 (11.9-86.0)	
Resistant	17	48.1(1.9-86.1)	0.11
Clinical response to firstline chemotherapy			
Yes	35	46.3(1.9-86.1)	
No	6	63.4(24.9-72.3)	0.11
BMI			
≤30	16	45.5 (1.9-86.0)	
>30	18	47.3(11.9-74.1)	0.2

Table 3: Relationship between serum Omentin -1 levels and clinicopathological variables of the patients group.

Visceral adipose tissue is not only an energy storage but also largest endocrine organ in the body[12]. It regulates energy homeostasis and other physiological processes by releasing adipokines. Leptin, adiponectin, apelin, visfatin, hepcidin, vaspin, and chemerin are adipokines. One of these adipokines, Omentin-1 (also named as omentin, İntelectin-1, endothelial lectin, HL-1 and intestinal lactoferrin receptor) is secreted predominantly by visceral adipose tissue[13,14].

Charasteristic	No. of events/n	12-month OS rate(%)	*P values*
Age, y			
≤55	2/17	100.0	
>55	13/24	78.6	0.01
Stage			
IIIC	11/29	84.9	
IIIV	3/10	87.5	0.52
Debalking status			
Optimal	9/28	91.8	
Suboptimal	5/12	71.6	**<0.001**
Tumor Histology			
Serous	11/36	79.6	
Non-serous	4/5	75	0.39
Operation timing			
PDS	11/31	88.4	
NACT-IDS	3/9	62.5	0.54
Clinical response to firstline chemotherapy			
Yes	Oct-35	93.3	
No	5/6	50	**<0.001**
Platin sensitive			
Sensitive	24-Apr	95.7	
Resistant	11/17	73.9	**0.007**
Serum Omentin level (U/L)			
Low (≤ median(46.6))	7/20	87.7	
High (>median(46.6))	8/21	78.2	0.91
Serum CA 125 level			
Normal	2/10	88.9	
High.	13/31	84.9	0.61
BMI			
≤30	5/17	84.4	
>30	5/17	81.4	0.8

Table 4: Univariate analysis of patients with epitelian ovarian cancerfor overall survival (OS) according to clinicopathological factors.

PDS: Primary debulking surgery, NACT-IDS: Interval debulking surgery after neoadjuvant chemotherapy, BMI: Body mass index

Studies investigating functions of omentin has lead to the discovery of its different actions like paracrine and endocrine effects to enhance insulin sensitivity and glucose metabolism[1].

Its role in supressing inflammation via activating AMPK/eNOS signalling pathway and inhibiting JNK pathway has been shown by Ohashi et al in obesity linked metabolic and cardiovasculer diseases[15].

Omentin was found to be decreased in patients with type 2 diabetes, obesity, impaired glucose tolerance and elevated blood pressure in clinical studies[16,17,7,15]. In vitro studies have shown that it exerts its modulatory effects to correct metabolic dysfunction via Akt activation leading to stimulation of glucose uptake[18]. Akt plays a crucial role in glucose metabolism, cell cycle and transcriptional regulation, apoptosis, and tumor progression[4]. Akt signalling has been shown to play a role in angiogenesis and tumorogenesis[5,6]. Previous studies have evaluated omentin-1 in policystic ovarian syndrome and documented its enhancing capacity in AKT phosphorylation / activation([7]. Thus, omentin has been thought to be a facilitator of carcinogenesis and has studied in colorectal cancer, renal cell cancer, prostate cancer and hepatocellular carcinoma[8,9,10,11]. However, whether there is an increase or decrease in omentin levels of cancer patients is not clarified as various studies yielded to different results. Shen XD et al showed significantly decreased omentin levels in patients with RCC when compared to healthy controls[9].

Recently, clinical research shows that cancers such as prostate and colorectal cancer were associated with increased omentin levels. Uyeturk et al compared omentin levels of patients with Benign Prostatic Hyperplasia (BPH) and prostate cancer (PCa)[8]. Fifty newly diagnosed patients with PCa and 30 patients with BPH were assesed for median omentin levels leading to 546.8 (297.1-945.6) ng/ml and 373 (207-792) ng/ml respectively[8]. As a result, omentin levels were found to be elevated in PCa. Another study by the same group showed increased levels of omentin in stage III Colorectal cancer patients treated with surgery and chemotherapy[19]. Circulating levels of omentin in patients with colorectal cancer (CRC) was studied by Fazeli et al and was found to be higher independent of measures of obesity. The authors attributed the increased omentin levels to the role of omentin in Akt pathway which is also important in progression of CRC by enhancement of cell proliferation activity and the blocking of apoptosis[20]. The Akt cascade activation leads to induction phosphotidyl inositol 3,4,5 triphosphates by phosphoinositide 3-kinase (PI3K)[21].

This induction of PI3K/Akt signalling promotes oncogenic ras-driven tumor growth[22].

The effect of omentin on hepatocellular carcinoma cell lines were evaluated and cell viability assay showed that omentin-1 significantly inhibited the proliferation of HCC cells, increased p21 and p53 and induced apoptosis[11].

In our study, we investigated the levels of omentin in patients with EOC and found significantly higher levels in contrast to control subjects irrespective of BMI, fasting plasma glucose, serum cholesterol, serum LDL, age, serum creatinine and blood pressure.

The increased levels of omentin in EOC patients in our study may be attributed to three hypotheses. Firstly, Activity of Akt pathway is related to cancer progression mechanisms, including proliferation, cell adhesion, apoptosis and transformation. This pathway is therefore thought to play a particularly important role in the pathogenesis of EOC. As omentin exerts its modulatory effects to correct metabolic dysfunction via Akt activation, increased levels of omentin may play an oncogenic role in EOC patients[23]. A second hypothesis based on a previously discussed study by Zang et al on HCC cell lines, can be that the omentin levels were increased as a protective mechanism in EOC patients in order to induce apoptosis of the tumor. A third hypothesis may consist of idea of omentin acting as a systemic hormone targetting endocrine organs like ovaries[24].

As, all of our patients were oopherectimized, omentin levels may have been increased due to continuous stimulation of adipose tissue by a rebound effect. However, the activity of omentin as an endocrine factor to modulate systemic metabolism should be evaluated further.

This study has the following limitations. Firstly, this is single-centre, study with a relatively small number of patients, and thus, cannot allow generalization of effects of omentin in EOC. Secondly, as we did not evaluate omentin levels in cell lines whether it exerts a protooncogenic or apopototic effect on EOC cells cannot be detected. Our hypothesis of omentin acting via Akt pathway was not supported by additional markers showing the activation of this pathway as we studied only omentin levels. The study group could not be subgrouped according to disease grade as it was a relatively small group. Thus, we could not evaluate the relationship between omentin levels and disease burden in EOC.

However, we found a positive correlation between CA125 and omentin levels of the patients. For this reason, we think that further studies evaluating the relation between disease status and omentin levels should be organized. Despite these limitations, this is the first comparative study that gives important data on relation between omentin levels and EOC. Further studies in order to establish the mechanism underlying Akt pathway and to assess the interaction between omentin and EOC are warrented.

In summary, these results indicated that serum Omentin-1 values were significantly elevated in patients with advanced ovarian carcinoma compared to healthy people.Because of positive correlation with CA-125, we may use the omentin in ovarian cancer in the future for treatment response and relaps status. For this reason, further studies with a greater number of patients are required to confirm the importance of serum Omentin-1 levels and changes in treatment duration with ovarian cancer.

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