

RESEARCH ARTICLE

Relations of Serum Visfatin and Resistin Levels with Endometrial Cancer and Factors Associated with its Prognosis

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Abstract

Background: The aims of this study were compare the serum visfatin and resistin levels between endometrial cancer (EC) patients and controls and evaluate their power to predict prognosis. **Materials and Methods:** This prospective study was conducted between March 2013 to June 2014 on the Gynecologic Oncology Department of the University of Selcuk, Konya, Turkey. A total of 42 EC patients and 42 controls were included and assessed for differences in serum visfatin and resistin levels, along with prognostic factors. **Results:** Endometrial cancer patients had significantly higher visfatin levels than controls (p: 0.011), associated with deep myometrial invasion (p: 0.019). In contrast the serum level of resistin did not significantly differ between EC patients and controls (p: 0.362). However, high resistin level in EC patients was associated with increase lymph node metastasis (p: 0.009). On logistic regression analysis, we found that serum visfatin elevation was associated with risk of myometrial invasion (OR: 1.091; 95% CI: 1.021- 1.166; p: 0.010) and serum resistin with risk of lymph node metastasis (OR: 1.018; 95% CI: 1.000- 1.035; p: 0.046). For myometrial invasion prediction, a serum visfatin level greater than 26.8 ng/mL demonstrated a sensitivity and specificity of 66.6 % and 96.4%, respectively. For lymph node metastasis prediction, the best cut-off for serum resistin level was 599ng/mL. A serum resistin level greater than this demonstrated a sensitivity and specificity of 87.5% and 77.1%, respectively. **Conclusions:** Our data suggest that serum visfatin is elevated in patients with EC and serum visfatin and resistin levels could be used to predict the risk of advance stage lesions.

Keywords: Visfatin - resistin - endometrial cancer - adipocytokine

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Introduction

Endometrial cancer (EC) is one of the most common gynecologic cancers in the world. According Globocan dates in 2012, approximately 320000 new cases were diagnosed all over the world. Endometrial cancer was diagnosed in 4.8% of women cancer and 2.1% of cancer depended death were attributed to EC (Ferlay et al., 2012; Bray et al., 2013). The main mechanism of endometrial cancer development is not explained clearly. Some of the risk factors for EC are obesity, hypertension, premature menarche and delay menopause (Braun et al., 2011; Parker et al., 1996). And potential biomarkers was described as EC prognosis (Zhu et al., 2012)

Obesity is an important environmental factor for EC development (Cote et al., 2013; Acmaz et al., 2014). Metabolic disorders including insulin resistance, hyperestrogenism, inflammation and impaired immunity are effects of increased body fat (Pilz et al., 2007).

Furthermore adipose tissue secretes many adipocytokines including visfatin and resistin (Galli et al., 2010). The role of adipocytokines in development of several cancer types was demonstrated in many studies (Nakajima et al., 2010; Dalamaga et al., 2012).

Visfatin is a 52kDa large protein and its gene located on chromosome 7q22.2. It was first suggested as an adipocytokine by Fukuhara et al. (2005). Visfatin gene is expressed in many tissues and visfatin was originally identified as pre-B-cell colony-enhancing factor (Sun et al., 2007). Recent studies suggest that visfatin has proinflammatory, insulin-like effects and relationship to metabolism, immune response and cancer (Moschen et al., 2007; Chang et al., 2010; Galli et al., 2010; Suhaimi et al., 2013). Over expression of visfatin has protective effect on cells from death by a specific pathway (Seetharam et al., 2006; Rajamohan et al., 2009). Visfatin is secreted from visceral fat and this molecule has role in obesity development (Stastny et al., 2012). Tian et al. (2013) was

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suggested visfatin may be a biomarker and prognostic factor for EC.

Resistin is a signal molecule secreted from adipocytes. It was first identified in obese mice. The major source of resistin is macrophages in humans and adipose tissues express in lower level. However, resistin levels are increased in obese humans. Resistin plays important role in various inflammatory processes (Rajala et al., 2002; Patel et al., 2003; Nohira et al., 2004). Furthermore resistin is also secreted from placenta, muscle, spleen, thyroid gland and uterus (Kusminski et al., 2005; Rzepka et al., 2014).

The relationships between EC and visfatin level was demonstrated in few studies (Luhn et al., 2013; Avcioglu et al., 2014). And the relationship between EC and resistin level was also demonstrated in different studies (Hlavna et al., 2011; Linkov et al., 2014). Also data related to the role and potential significance of adipokines in EC are limited. None has previously tested the joint effects of serum visfatin and resistin on the risk of development of metastasis in women with EC. The impact of serum visfatin and resistin together on EC metastasis is yet unknown.

Recent findings suggest that adipocytokines may play important role in carcinogenesis in EC. The first aim of this study is compare the serum visfatin and resistin level between EC patients and control group. And the second is evaluation the power of serum visfatin and resistin levels on the prediction of prognostic factors of EC patients.

Materials and Methods

This prospective study was conducted between March 2013 to June 2014 on the Gynecologic Oncology Department of The University of Selcuk, Konya, Turkey. The study protocol was approved by the Ethics Committee of the University Hospital and informed consent was obtained from each participant.

Patients who will have endometrial cancer which was proven by endometrial sampling were candidates for our study. Control group includes healthy volunteers who applied gynaecology clinic for abnormal bleeding and endometrial cancer was excluded by endometrial sampling. Chronic renal failure, uncontrolled hypertension, liver impairment, cardiovascular disease, uncontrolled diabetes mellitus, morbid obesity and statin medication constituted the exclusion criteria for control and EC group. None of the patients in EC group has undergone radiotherapy or chemotherapy before surgery.

EC group was consisted of 49 subjects and seven patients were excluded from study because of chronic diseases. Forty-two patients were included in the EC group. The numbers of patients in EC and control group were 42 in both groups.

After registration, age, gravida, body mass index (BMI), serum visfatin and resistin levels and medical history were noted. Detailed physical examination and pelvic examination were performed for each participant. The woman's height, weight and the body mass index (BMI) was calculated. Routine laboratory testing was performed before surgery and endometrial sampling.

Serum samples were collected before surgery and collected samples were centrifuged and stored at -80°C. Serum visfatin and resistin levels were measured by using Enzyme- Linked Immuno Sorbent Assay (ELISA) kit (Eastbiopharm, China) according to manufacturer's protocol on Rayto- 2100C Microplate Reader (India).

Statistical analysis

The Kolmogorov-Smirnov normality test was used to determine the distribution pattern of the variables. Log transformations were performed on non-parametric variables. Comparison between the resistin and visfatin levels in EC and control group was made by using t- tests. Differences between categorical variables were analyzed by Chi square test. Fisher's exact test was used when Chi square test conducted for values with an expected frequency of 5 or less. Correlation analysis was performed for calculation of association of serum visfatin and resistin levels and other parameters. Relationships between variables were analyzed using Pearson's or Spearman's rank correlation coefficients. The relation between visfatin and risk of myometrial invasion and resistin and risk of lymph node metastasis were assessed using logistic regression analysis. Receiver operator characteristic (ROC) analysis and calculation of area under the curve (AUC) were also performed for myometrial invasion and lymph node metastasis. A p value less than 0.05 was considered statistically significant. The statistical analysis was carried out by using Statistical Package for the Social Science (SPSS), version 15.0 (SPSS Inc., Chicago, IL, US). A P-value of <0.05 was considered as statistically significant.

Results

There was no difference between EC patients and control group in age, gravida, BMI, hypertension and diabetes mellitus rates. When compared serum visfatin and resistin level, endometrial cancer patients had significantly higher visfatin level than control group the mean values were 14.9 ± 10.6 ng/mL and 8.1 ± 6.9 ng/mL respectively (p:0.011). There was no difference between groups resistin levels.

The FIGO stage of 21 (50%) patients was IA, 9 (21.4%) patients was IIA, 5(11.9%) patients was II, 6 (14.3%) patients was IIIC and 1 (2.4%) patient was IV. The grade of EC patients was grade 1 in 25 (59.5%) patients, grade 2 in 13 (31%) patients and grade 3 in 4 (9.5%) patients. Fourteen (33.3%) patients have invasion of more than one-half of the myometrium. Lymph node metastasis was observed in 7 (16.7%) patients. In EC patient's serum visfatin and resistin levels were compared for prognostic factors such as myometrial invasion, lymph node metastasis, grade and tumor size. According to correlation analysis there was no correlation with tumor size, Ca 125 level and tumor grade in EC group. Serum resistin level was significantly correlated with BMI in total participants (r: 0.274, p:0.012). Serum visfatin level was significantly correlated with myometrial invasion and serum resistin level was significantly correlated with lymph node metastasis (r: 0.350, p:0.023 and r: 0.490, p:0.001 respectively) (Table 1).

Patients who have invasion of less than one-half of the myometrium, the mean visfatin level was 10.6 ± 7.6 ng/mL and the patients who have invasion of more than one-half of the myometrium, the mean visfatin level was 23.5 ± 16.2 ng/mL in patients group. The difference was statistically significant ($p:0.019$). Patients who have invasion of less than one-half of the myometrium the mean resistin level was 467.3 ± 354.9 ng/mL and the patients who have invasion of more than one-half of the myometrium, the mean resistin level was 374.6 ± 348.9 ng/mL. However the differences between resistin levels were not significantly different according to myometrial invasion ($p:0.362$). Patients who have lymph node metastasis the mean resistin

level was 881.4 ± 340 ng/mL and the patients who have not lymph node metastasis the mean resistin level was 347.44 ± 304.9 ng/mL. The difference was statistically significant ($p:0.009$). Visfatin levels were not significantly different according to lymph node metastasis ($p:0.896$) (Table 2).

ROC analysis of visfatin levels according to myometrial invasion and resistin levels according to lymph node metastasis were performed in patient's group. In our study, best cut-off for visfatin level was 26.75 ng/mL for myometrial invasion prediction. For myometrial invasion prediction, serum visfatin level greater than 26.75 ng/mL demonstrated a sensitivity and specificity of 66.6% and 96.4% respectively (ROC AUC: 0.714 ; 95% CI: $0.526-0.903$). The positive predictive value was 87.5% and negative predictive value was 80% (Figure 1). For lymph node metastasis, the best cut-off for serum resistin level was 599 ng/mL. Serum resistin level greater than this level demonstrated a sensitivity and specificity of 87.5% and 77.1% respectively (ROC AUC: 0.878 ; 95% CI: $0.705-1.000$). The positive predictive value was 46.6% and negative predictive value was 97.2% (Figure 1).

Using binary logistic regression analysis, we found that serum visfatin level was associated with risk of myometrial invasion (OR: 1.091 ; 95% CI: $1.021-1.166$; $p:0.010$) and serum resistin level was associated with risk of lymph node metastasis (OR: 1.018 ; 95% CI: $1.000-1.035$; $p:0.046$). We found that visfatin is an independent

Table 1. Pearson's Correlation Result between Serum Visfatin and Resistin Levels with Clinical and Laboratory findings

Variables	Visfatin		Resistin	
	r	p	r	p
Age (n= 84)	0.156	0.157	0.153	0.165
BMI (n= 84)	0.078	0.479	0.274	0.012*
Tumor size ^y (n= 42)	0.033	0.834	0.126	0.428
Ca 125 ^y (n= 42)	0.163	0.275	0.007	0.963
Grade ^y α (n= 42)	0.122	0.443	0.198	0.209
MI ^y α (n= 42)	0.350	0.023*	-0.168	0.289
LNM ^y α (n= 42)	-0.058	0.715	0.490	0.001*

*MI: Myometrial invasion, LNM: Lymph node metastasis, ^yEndometrial cancer patients, α Spearman's correlation analysis, *means $p < 0.05$

Table 2. Correlation of Serum Marker Levels with prognostic factors

Variables	Myometrial invasion		t	p
	<1/2 (Mean±SD)	>1/2 (Mean±SD)		
Visfatin	10.6 ± 7.6	23.5 ± 16.2	-2.452	0.019*
Resistin	467.3 ± 354.9	374.6 ± 348.9	0.923	0.362
Variables	Lymph node metastasis		t	p
	Positive (Mean±SD)	Negative (Mean±SD)		
Visfatin	13.4 ± 11.5	15.2 ± 12.9	0.132	0.896
Resistin	881.4 ± 340	347.4 ± 304.9	-2.765	0.009*

*Min: Minimum; Max: Maximum, *means $p < 0.05$

Table 3. Relationships of Various Factors with Myometrial Invasioun and Lymph Node Metastasis

Variables	Binary logistic regression					
	MI			LNM		
	OR	95% CI	P	OR	95% CI	P
Visfatin (ng/mL)	1.091	1.021-1.166	0.010*	0.901	0.746-1.088	0.941
Resistin (ng/mL)	0.999	0.996-1.001	0.416	1.018	1.000-1.035	0.046*
Age (year)	1.021	0.945-1.104	0.594	0.941	0.779-0.136	0.524
BMI (kg/m ²)	1.045	0.848-1.286	0.682	1.344	0.719-2.512	0.355
Ca 125 (ng/mL)	1.019	0.994- 1045	0.131	1.009	0.993-1.025	0.277
HT	0.447	0.056-3.584	0.448	3.340	1.026-15.495	0.014*
DM	0.521	0.049-5.595	0.590	1.038	0.794-1.230	0.186

MI: myometrial invasion; LNM: Lymph node metastasis; OR: Odds ratio; CI: Confidence interval; BMI: Body- mass index; HT: Hypertension; DM: Diabetes mellitus means $p < 0.05$

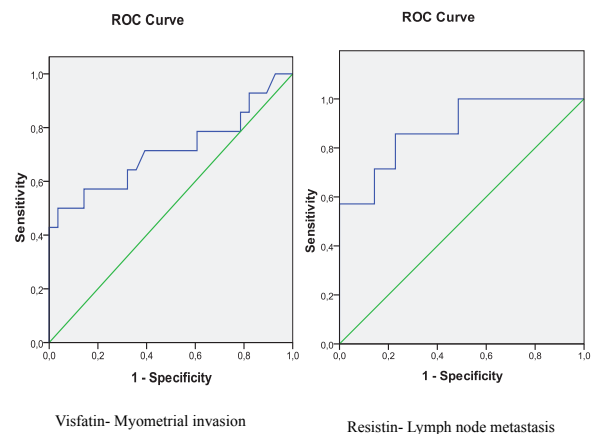


Figure 1. ROC Analysis of the Myometrial Invasion Prediction of Visfatin. AUC=0.714; 95%CI=0.526-0.903
ROC analysis of the lymph node metastasis prediction of resistin. AUC=0.878; 95% CI=0.705-1.000

risk factor for myometrial invasion and resistin is an independent risk factor for lymph node metastasis in endometrial cancer patients (Table 3).

Discussion

Endometrial carcinoma usually occurs in postmenopausal patients. The mean age of EC at diagnosis is 61 years (Howlander et al., 2014). In our study the mean age of patient's group was 60 and it was compatible with literature. Obesity and chronic anovulation are risk factors for premenopausal EC. Many studies have shown that obesity increases the risk of EC (Braun et al., 2011; Cote et al., 2014; Secilmis et al., 2014). A meta-analysis suggested that each increase in BMI of 5 kg/m² induce 1.59 fold increasing in endometrial cancer risk. It was determined that serum visfatin level was higher in obese patients (Renehan et al., 2008). There have been conflicting data of correlation between obesity and serum visfatin and resistin level. Although some initial studies suggested positive correlation between obesity and serum visfatin and resistin levels, several other studies have failed to confirm this finding (Azuma et al., 2003; Amirhakimi et al., 2011). The correlation between BMI and serum visfatin level was not observed in present study. And the difference between two study groups was also not significant. A weak correlation between serum resistin level and BMI was observed (r: 0.274, p:0.012).

Luhn et al. suggested that adipokine levels influence EC risk. Although, serum visfatin level was higher in EC patients, no association between serum visfatin level and EC was determined in that study. However, Luhn et al (2013) report has its inherent limitation such as inadequate sampling of serum visfatin was declared by authors as limitation of that study. The important role of visfatin on carcinogenesis and cancer progression was discussed in a study from China concludes that visfatin has an important role in carcinogenesis and cancer progression (Bi and Che, 2010). In our study, in line with this report serum visfatin level was significantly higher in EC patients.

Tian et al. (2013) suggested that high visfatin level was associated with advance myometrial invasion and visfatin level has prognostic effect on endometrial cancer patients. Avcioglu et al. (2014) conducted a study and concluded that visfatin was important risk factors for occurrence of EC other than age, BMI and diabetes. However, prognostic importance of visfatin was not determined in that study. These conflicting results may be due to small number of participants. According to our results, higher serum visfatin level has not only increase risk for endometrial cancer but also has been independent risk factor for deep myometrial invasion. Myometrial invasion is an important prognostic factor for EC (Havrilesky et al., 2005). Preoperative determination of endometrial invasion is challenging issue for clinicians. Tian et al. (2013) suggested that higher serum visfatin level was an independent risk factor for EC and he also suggested that high visfatin expression in EC tissue was associated with deep myometrial invasion. Serum visfatin level higher than 12.5 ng/mL was a predictor for EC. In our study the mean serum visfatin level was 14.9±10.6 ng/mL in EC

group and mean serum visfatin level was 8.1±6.9 ng/mL in control group. According to our data serum visfatin level greater than 26.7 ng/mL demonstrates high myometrial invasion rates with sensitivity and specificity of 66.6% and 96.4% respectively. Serum visfatin level greater than 26.75 ng/mL was highly correlated with myometrial invasion level (OR: 1.091; 95%CI: 1.021- 1.166; p:0.010).

Several mechanisms were described for pathophysiologic pathway for resistin to cancer progression. Resistin can increase cell proliferation by inducing phosphatidylinositol 3-kinase or it could be act as specific receptor inducers (Tarkowski et al., 2010; Kim, 2011). Hlavna et al. (2011) conducted a study about resistin levels and EC. According to this study EC patient has significantly higher resistin level than control group. In our study there was no significantly difference between serum resistin levels of EC patients and control patients. The role of resistin on cancer dissemination by the effecting cell adhesion molecule was evaluated on hepatocellular carcinoma patients (Yang et al., 2014). In that study it was shown that resistin induced the expression of adhesion molecules, including ICAM-1 and VCAM-1 in the endothelial cells. It has been shown that elevated adhesion molecules expressions are associated with advance disease stage and poor prognosis (Alexiou et al., 2001; Kobayashi et al., 2007). Present study demonstrated that serum resistin level could be used as a predictor for lymph node metastasis. Higher resistin levels were independent risk factor for lymph node metastasis (OR: 1.018; 95%CI: 1.000- 1.035; p:0.046). Serum resistin level greater than 599 ng/mL demonstrates higher lymph node metastasis rates. It could be hypothesised that elevated resistin level is associated with advance disease stage and poor prognosis. To our knowledge, this is the first study that demonstrates serum resistin level as a predictor for lymph node metastasis in EC.

Our study has some limitations. First, this study was performed on a relatively small group and in a single institute. We could not demonstrate the effect of high visfatin and resistin on survival of endometrial cancer due to the short time course. In this study we could not evaluate other adiponectins, oxidative stress markers and inflammatory markers including IL- 1, IL- 6 and IL- 8 levels and we used only single measurement of serum visfatin and resistin level, which may cause to error regarding to miscalculation.

Our data suggest that serum visfatin level is elevated in patients with EC and serum visfatin and resistin levels could be predict the risk of advance stage in women with EC. The exact mechanisms of visfatin and resistin on cancer development are unclear. High number of cases with level of oxidative stress markers, inflammatory markers and other adiponectin required to determine the diagnostic and prognostic value of visfatin and resistin on endometrial cancer.

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