# Discriminative Ability of Estimated Serum Levels of YKL-40 and Adiponectin for the Presence of Endometrial Carcinoma

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**Abstract: Objectives:** To estimate serum YKL-40, leptin and adiponectin (APN) levels in women had gynecological pathologies and to evaluate its predictability for the presence of endometrial carcinoma (EC). **Patients & Methods:** Forty-one uterine myoma (UM) patients, 21 EC patients and 13 endometriosis (EM) patients were diagnosed after complete clinical, endoscopic and radiological examination. Fifteen age- and body mass index matched women free of malignancy and other morbidities were included as control group for the results of laboratory investigations. Patients and controls gave fasting venous blood samples for ELYSA estimation of APN, leptin and YKL-40 serum levels. Patients received the appropriate therapy according to the final diagnosis. **Results:** Serum YKL-40 and leptin levels were significantly higher while serum APN levels were significantly lower in patients compared to controls. Serum YKL-40 and leptin levels were significantly higher and serum APN levels were significantly lower in EC patients than in UM and EM patients. Serum YKL-40 levels were significantly higher; while serum leptin levels were non-significantly higher and serum APN levels were non-significantly lower in EM patients compared to UM patients. Regression analysis defined high serum YKL-40, low serum APN and high serum leptin as differentiating predictor for EC, while only high serum YKL-40 as significant predictor for EM. **Conclusion:** Disturbed serum adipo-cytokines showed significant relationship with the development or progression of gynecological pathologies. Elevated serum YKL-40 could be used for discrimination of EC and EM patients. Lower serum APN levels could be used as a significant predictor for presence of EC, so a diagnostic panel of estimation of serum YKL-40 and APN could define EC patients.

**Keywords:** Endometrial carcinoma, Endometriosis, YKL-40, Adiponectin, Leptin

## 1. Introduction

Female genital tract is most common site for tumors in females *(Ramesh et al., 2013).* Endometrial carcinoma (EC) is the most common gynecological cancer *(Morice et al., 2016)* and has increased 21% in incidence since 2008 with increased death rate by more than 100% over the past two decades. The observed rise in incidence is mainly caused by life style factors including obesity and diabetes *(Salehi et al., 2015).* Precursor lesions of complex hyperplasia with atypia are associated with EC in more than 40% of cases *(Sorosky, 2012).*

The mainstay of the initial treatment for EC is surgery with total hysterectomy and bilateral salpingo-oophorectomy. Pelvic-aortic lymphadenectomy may be appropriate for patients having tumors with a high risk for extrauterine spread *(Loukovaara et al., 2014).* However, preoperative imaging cannot accurately assess lymph node involvement and gross examination of depth of myometrial invasion does not have accurate predictability to select women who can have lymphadenectomy safely omitted from the surgical procedure *(Sorosky, 2012).*

Adiponectin (APN) is insulin-sensitizing protein that is secreted from adipose tissue *(Erdogan et al., 2013).* APN dysregulation is postulated to affect cancer risk via modulation of insulin resistance and inflammation *(Beg et al., 2015).* Lower plasma APN concentration was related to an increased incidence and may act as an independent predictor for clear cell renal cell carcinoma *(Wang et al., 2016)*, the development of colorectal adenoma *(Name et al., 2016)* and serum APN levels was inversely correlated with leukemia and can be used as an effective biologic marker in early diagnosis and therapeutic monitoring of leukemia *(Ma et al., 2016).*

Leptin is a single-chain proteohormone that plays a key role in the regulation of body weight *(Webber, 2003).* Leptin is produced by differentiated adipocytes, although production has been demonstrated in other tissues *(Baratta 2002).* Leptin receptors are found ubiquitously in the body *(Tsiotra et al., 2000)*, but a circulating form of leptin receptor exists *(Lammert et al., 2001).*

Leptin/leptin receptor dysregulation have a role in the development of a large variety of malignancies including breast, thyroid, endometrial and

gastrointestinal malignancies, predominantly through the Janus kinas signal transducer of activators of transcription signaling pathway *(Mullen and Gonzalez-Perez, 2016)* which regulates downstream signaling pathways such as expression of antiapoptotic proteins and systemic inflammation *(Dutta et al., 2012)*, angiogenic factors and pro-proliferative molecules *(Rene et al., 2009)*, hypoxia inducible factor-1a expression *(Dutta et al., 2012)* and phosphoinositide 3-kinase/protein kinase B signaling and extracellular signal-regulated kinase 2 *(Uddin and Mohammad, 2016).*

YKL-40 (chitinase-3-like-1) is a 40 kDA glycoprotein *(Metllinos-Katsaras, 2012),* produced by immunologically active cells such as macrophages and neutrophils and is a highly conserved serum protein *(Elshorbagy et al., 2012).* YKL-40 is known to stimulate growth of fibroblast cells, exerts anti-apoptosis action, functions in angiogenesis, is a potent migration factor for endothelial cells, and may take part in the innate immune response *(Maggio et al., 2012).* High plasma concentrations of YKL-40 are found in patients with diseases characterized by inflammation or increased tissue remodeling or with cancer *(Zhu et al., 2002).*

The current study aimed to estimate serum YKL-40, leptin and APN in women had gynecological pathologies and to evaluate its predictability for the presence of EC.

## 2. Patients & Methods

The current prospective study was conducted at Obstetrics and Gynecology Department in conjunction with Clinical Pathology Department at Al-Salam Saudi Hospital, Saadah, Yemen; since March 2012 till April 2016. The study protocol was approved by Local Ethical Committee. Written fully informed consent for study participation was signed by patients. Patients were selected out of those attending the Gynecology outpatient clinic complaining of symptoms suggestive of having either uterine myoma (UM), endometriosis (EM) or EC.

Forty-one uterine myoma (UM) patients, 21 EC patients and 13 endometriosis (EM) patients were diagnosed after complete clinical, endoscopic and radiological examination. Fifteen age- and body mass index matched women free of malignancy and other morbidities were included as control group for the results of laboratory investigations. Patients and controls gave fasting venous blood samples for ELYSA estimation of APN, leptin and YKL-40 serum levels. Patients received the appropriate therapy according to the final diagnosis.

Uterine myoma patients were mostly presenting by heavy menstrual bleeding, pelvic pressure manifestations or pelvic, back or leg pain or being asymptomatic and discovered during routine examination. Patients with suspected UM on pelvic examination underwent abdominal and transvaginal ultrasound examination; hysteroscopy and MRI imaging if required. Endometrial carcinoma patients mostly were presented by abnormal vaginal bleeding, profuse vaginal discharge, pain with urination and sex, and pelvic pains. Patients with suspected EC underwent ultrasound examination and hysteroscpic biopsy taking for histological examination and staging. Then, chest X-ray and CT and MRI imaging was conducted for detection of metastasis. Endometriosis (EM) was diagnosed during laparoscopic examination for pain, infertility or other benign gynecological disorders and was confirmed histologically. All enrolled EM women had regular menstrual cycles and none of them took medication that affect hormonal or immunological status within 3 months before laparoscopy, or had undergone surgical treatment for EM within 1 year. All patients received the appropriate therapy according to the final diagnosis.

All patients underwent full history taking included age, body mass index (BMI) data, parity and number of living offspring, disease-related history and presence of medical co-morbidities. Patients had a history of diabetes, liver, vascular or neoplastic disorders were excluded from the study. The study also included 15 age-and BMI-matched women free of malignancy and other morbidities who gave blood samples as control group for the results of laboratory investigations.

## Laboratory Investigations

Fasting venous blood samples were obtained under complete aseptic conditions from the antecubital vein. The collected blood sample was put in a plane container and left to clot at room temperature for 30 minutes before centrifugation for 20 minutes at 1,000g. Freshly prepared serum was stored at $-20^{o}C$ till ELYSA estimation of adiponectin (Abcam's Human Adiponectin ELISA, San Francisco, USA) *(Yokota et al., 2000)*, leptin (Abcam's Human Leptin ELISA, San Francisco, USA) *(Havel et al., 1996),* and YKL-40 levels (Human Chitinase 3-like 1/YKL-40 PicoKine ™ ELISA Kit, Valley Ave, Pleasanton, USA) *(Shackelton et al., 1995).*

## Statistical Analysis

Obtained data were presented as mean±SD, ranges, numbers and percentages. Results were analyzed using One-way ANOVA with post-hoc Tukey HSD Test and Chi-square test ($X^2$ test). Possible relationships were investigated using Spearman linear regression. Sensitivity & specificity of estimated parameters as predictors were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) compared versus the null hypothesis that

AUC=0.05. Regression analysis (Stepwise method) was used for stratification of studied parameters as significant predictors for the target disease. Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value <0.05 was considered statistically significant.

## 3. Results

The study included 75 patients with variant gynecological pathology; 41 patients (54.7%) had UM, 21 patients (28%) had EC and 13 patients (17.3%) had EM. Mean age of studied patients was 58.9±7; range: 45-73 years; but majority were older than 50 years. Mean BMI of studied patients was 31.6±3.3; range: 26.3-38.3 kg/m$^2$; 43 patients (57.3%) were obese and 32 patients (42.7%) were overweight. Details of enrollment data of studied patients showed non-significant (p>0.05) difference compared to control women as shown in table 1.

**Table (1):** Patients' enrollment data

| Data | | | Control | Patients | P value |
|---|---|---|---|---|---|
| Age (years) | Strata | <50 | 2 (10%) | 12 (16%) | NS |
| | | 50-59 | 5 (25%) | 26 (34.7%) | |
| | | 60-69 | 7 (35%) | 33 (44%) | |
| | | ≥70 | 1 (5%) | 4 (5.3%) | |
| | Total | | 59.5±7.1 | 58.9±7 | NS |
| BMI data | Body weight (kg) | | 88.5±7.7 | 91.2±10.9 | NS |
| | Body height (cm) | | 171±3.1 | 169.8±3.3 | NS |
| | BMI (kg/m$^2$) | <30 | 7 (46.7%) | 32 (42.7%) | NS |
| | | ≥30 | 8 (53.3%) | 43 (57.3%) | |
| | | Total | 30.3±2.6 | 31.6±3.3 | NS |
| Parity | | | 3.1±0.7 | 3.7±1.1 | NS |

Data are presented as numbers & mean±SD; percentages are in parenthesis

Mean patients' serum YKL-40 levels were significantly (P1=0.001) higher compared to control levels. Moreover, serum YKL-40 levels in EC patients were significantly higher than in patients had UM (P2=0.001) and EM (P3=0.005) with significantly (P2=0.048) higher levels in EM patients compared to UM patients (Fig. 1).

Mean serum leptin levels were significantly (P1=0.001) higher in EC patients compared to control levels, but were non-significantly (P1>0.05) higher in patients had UM and EM compared to control levels. Moreover, serum leptin levels in patients had EC were significantly higher than in patients had UM (P2=0.001) and EM (P3=0.008), but were non-significantly (P2>0.05) higher in patients had EM compared to UM patients (Fig. 2).

Mean patients' serum APN levels were significantly (P1=0.001) lower compared to control levels. Mean serum APN levels were significantly lower in EC patients compared to patients had UM (P2=0.001) and EM (P2=0.014) with non-significantly (P3>0.05) lower levels in EM patients compared to UM patients (Table 2, Fig. 3).

**Table (2):** Mean serum levels of studied parameters estimated in enrolled patients categorized according to pathological lesion and compared to control women

| Group Parameter | | Control | Patients | | | |
|---|---|---|---|---|---|---|
| | | | UM | EC | EM | Total |
| YKL-40 (pg/ml) | Mean | 22.7±7.3 | 109.5±40.3 | 194.2±84.5 | 133.6±26.6 | 137.4±65.36 |
| | P1 | | 0.001 | 0.001 | 0.001 | 0.001 |
| | P2 | | | 0.001 | 0.048 | |
| | P3 | | | | 0.005 | |
| Leptin (ng/ml) | Mean | 4.72±2.4 | 7.65±3.5 | 23.63±20.1 | 11.64±7.53 | 12.8±13.15 |
| | P1 | | NS | 0.001 | NS | NS |
| | P2 | | | 0.001 | NS | |
| | P3 | | | | 0.008 | |
| APN (μg/ml) | Mean | 16.62±2.33 | 13.34±2.77 | 10.47±1.84 | 13±1.14 | 12.5±2.6 |
| | P1 | | 0.001 | 0.001 | 0.001 | 0.001 |
| | P2 | | | 0.001 | NS | |
| | P3 | | | | 0.014 | |

Data are presented as mean±SD; UM: Uterine myoma; EC: Endometrial carcinoma; EM: Endometriosis; APN: Adiponectin; P1: significance of difference versus control group; P2: significance of difference versus UM group; P3: significance of difference versus EC group; NS: Non-significant difference; P<0.05: significant difference.
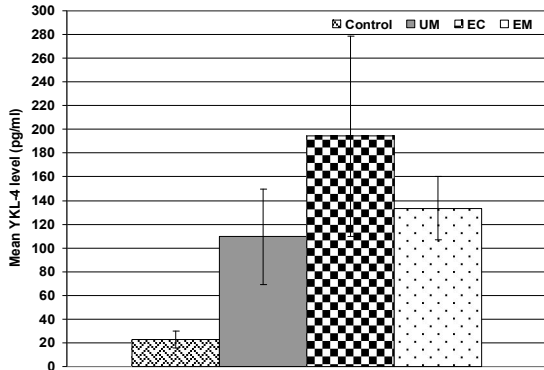


Fig. (1): Mean (±SD) serum YKL-4 level estimated in patients categorized according to pathological lesion
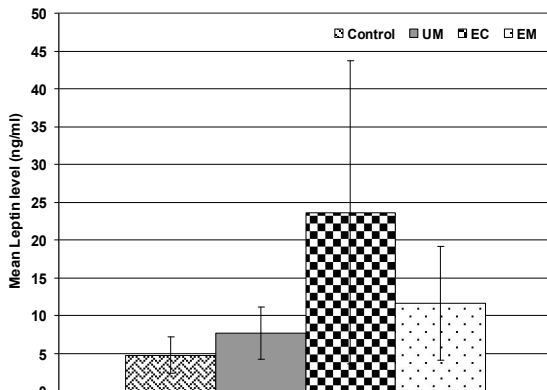


Fig. (2): Mean (±SD) serum Leptin level estimated in patients categorized according to pathological lesion
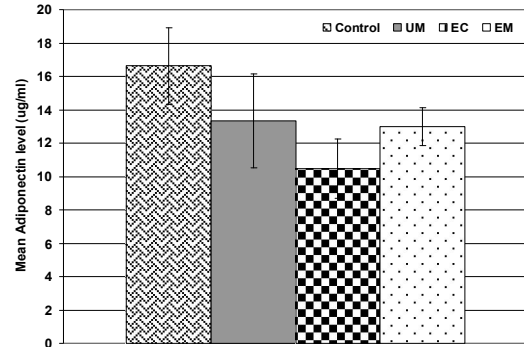


Fig. (3): Mean (±SD) serum adiponectin level estimated in patients categorized according to pathological lesion

Estimated serum levels of studied adipo-cytokines showed significant correlation with the presence of EC. Such correlation was positive with serum YKL-40 (Rho=0.514, p<0.001) and leptin (Rho=0.454, p<0.001), but was negative (Rho=-0.47, p<0.05) with serum level of APN. ROC curve analysis defined high serum levels of YKL-40 and leptin and low serum APN as significant (p<0.001) predictors for presence of malignancy with AUC=0.830, 0.792 and 0.198, respectively (Fig. 4). However, Regression analysis defined high serum YKL-40 levels as significant predictor for the presence of EC in three models, low serum APN in two models and high serum leptin in one model (Table 3).
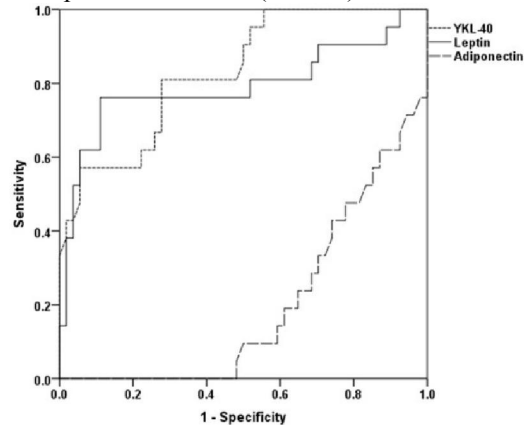


**Fig. (4): ROC curve analysis of estimated levels of serum adipo-cytokines as predictors of presence of endometrial carcinoma**

**Table (3): Regression analysis of estimated parameters as predictors for presence EC in the enrolled patients**

| Statistical model no. | Parameter | β | t | Sig. |
|---|---|---|---|---|
| One | Serum YKL-40 | 0.409 | 4.879 | <0.001 |
| | Serum APN | -0.317 | 3.757 | 0.001 |
| | Serum leptin | 0.317 | 3.665 | 0.001 |
| Two | Serum YKL-40 | 0.478 | 5.399 | <0.001 |
| | Serum APN | -0.399 | -4.509 | <0.001 |
| Three | Serum YKL-40 | 0.546 | 5.565 | <0.001 |

Evaluation of estimated adipo-cytokines for discrimination between patients had EM out of patients had gynecological problems using ROC curve analysis as shown in figure 5, defined high serum YKL-40 (AUC=0.776, p=0.003) and leptin (AUC=0.720, p=0.017) levels as significant predictors for presence of EM; while low serum APN failed to be a significant predictor (AUC=0.497, p>0.05). Regression analysis defined high serum YKL-40 as a significant predictor in two models (β=0.338 & 0.344, p=0.011) and high serum leptin (β=0.261, p=0.044) in one model.
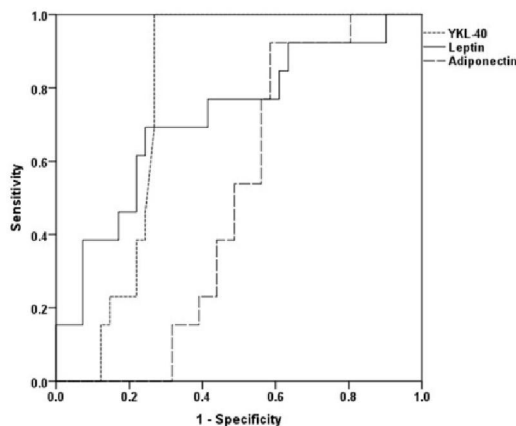


**Fig. (5): ROC curve analysis of estimated levels of serum adipo-cytokines as predictors of presence of endometriosis**

## 4. Discussion

The current study reported a definite association between development of gynecological pathologies and disturbed serum levels of adipo-cytokines, where serum levels of YKL-40 and leptin were significantly higher while serum levels of APN were significantly lower in patients, irrespective of the underlying pathology, compared to control women of comparable age and BMI and were free of gynecological pathologies.

The obtained results indicated a possible relationship between disturbed serum levels of adipo-cytokines and systemic diseases not related to or governed in its pathogenesis and/or progression by adiposity and go in hand with *Pham et al. (2013)* who found that serum adipokine levels differentially correlate with β-cell function in type 1 diabetes independent of BMI or metabolic control. Also, *Bustos Rivera-Bahena et al. (2015)* detected that circulating leptin, resistin, interleukin (IL)-6 and IL-17 levels positively correlate, independently on BMI, with rheumatoid arthritis clinical activity and concluded that other metabolic or inflammatory factors could be involved in pathogenesis or progression of rheumatoid arthritis. Recently,

*Gumanova et al. (2016)* found leptin/insulin and APN/endothelin ratios are novel biomarkers useful for noninvasive diagnosis of initial stages of coronary lesions in patients with coronary artery disease.

Moreover, the obtained results go in hand with multiple previous studies reported a possible relation between disturbed serum levels of adipo-cytokines and variant gynecological and obstetric problems wherein *Al-Kholy et al. (2010)* reported significantly higher serum retinol binding protein-4 levels in women with pre-eclampsia (PE) and that its levels were positively correlated with PE severity clinical markers. Also, *Al-Nory et al. (2011)* reported that estimation of serum soluble endoglin at 12th week of gestation could be used as a sensitive screening test for women liable to development of PE. Recently, *Song et al. (2016)* documented that leptin and resistin play important roles in the onset of PE, and may have some impacts on the fetal growth and development. On the other hand, *Wickham et al. (2011)* found women with polycystic ovary syndrome (PCOS) have lower total and high-molecular weight APN levels compared with healthy women and *Chen et al. (2015)* suggested that adipose tissue might play an important role in the metabolic complications in women with PCOS.

Concerning discrimination of EC patients among studied women with variant gynecological problems; serum YKL-40 and leptin levels were significantly higher and serum APN levels were significantly lower in EC patients than in patients who had UM and EM. Regression analysis defined high serum YKL-40, low serum APN and high serum leptin as differentiating predictor for EC among variant gynecological pathologies, in decreasing order of significance.

Unfortunately, no previous single prospective study evaluated the three parameters for predictability of presence of EC. However, the obtained data supported that previously reported for each parameter separately; where *Soliman et al. (2006)* found women with EC were more likely to have low APN levels than controls and APN level was independently and inversely associated with EC. Also, *Cust et al. (2007)* found high circulating APN levels, independent of other obesity-related risk factors, are associated with reduced EC risk. Thereafter, *Erdogan et al. (2013)* showed that lower levels of circulating APN and vaspin are associated with an increased risk of developing EC. *Dallal et al. (2013)* reported that leptin-BMI axis might increase EC risk through mechanisms other than estrogen-driven proliferation and *Wang et al. (2014)* suggested that high leptin level is an independent risk factor of EC.

Also, *Fan et al. (3013,2014)* reported significantly higher pre-operative serum YKL-40 values in EC cases than that in UM cases and in

healthy women and in multivariate analysis, elevated serum YKL-40 significantly correlated with FIGO stage and tumor grade *(Fan et al., 2014)*. Moreover, mean postoperative serum YKL-40 levels were significantly lower than preoperative levels in EC cases with significantly shorter progression-free survival and overall survival for the YKL-40-positive patients than for the YKL-40-negative patients *(Fan et al., 2013)*. *Cheng et al. (2014)* documented that circulating YKL-40 could be promising and meaningful in the diagnosis of EC.

Recently, *Zheng et al. (2015)* demonstrated that low level of circulating APN is a risk factor for EC. Also, *Gong et al. (2015)* suggested that increased circulating APN or decreased leptin concentrations were associated with reduced risk of EC. Moreover, *Lin et al. (2015)* and *Zeng et al. (2015)* suggested that higher APN levels might have a protective effect against EC, especially in postmenopausal women.

In 2016; *Li et al. (2016)* through a systemic review documented that low circulating APN level increases the risk of EC, whereas the high APN level decreases this risk in postmenopausal women and circulating APN as simple biomarkers may be a promising tool for the prevention, early diagnosis and disease monitoring of EC. *Kemik et al. (2016)* found YKL-40 and human epididymis secretory protein 4 were significantly higher in patients with EC and so may be used for early determination of EC and detection of high risk subsets before surgery.

As regards to discrimination of EM patients out of patients who had gynecological pathologies other than EC, high serum YKL-40 showed significant discriminative ability over leptin, while low serum APN levels failed to show discriminative ability. In line with these findings, *Kim et al. (2010)* using immunohistochemistry reported that YKL-40 is related to severity of peritoneal EM. *Tuten et al. (2014)* documented that YKL-40 may be utilized as a marker for determining the severity of endometriosis and *Ural et al. (2015)* detected increased serum YKL-40 levels in patients with EM compared to controls and proposed that circulating YKL-40 levels could be a novel biomarker for diagnosis and follow-up of endometriosis.

## Conclusion

Disturbed serum adipo-cytokines showed significant relationship with the development or progression of gynecological pathologies. Elevated serum YKL-40 could be used for discrimination of EC and EM out of other pathologies. Lower serum APN levels could be used as a significant predictor for presence of EC. A diagnostic panel of estimation of serum YKL-40 and APN could define EC patients, but its use as a screening test for high-risk women needs further wide-scale study for confirming such applicability and defining a suitable cutoff point for this purpose.

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