Serum Leptin / Adiponectin Ratio: A Possible Marker of Endometrial Pathologies in patients with Postmenopausal Bleeding

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Abstract: Objectives: The aim of the study was to evaluate serum leptin / adiponectin ratio as a marker for endometrial pathologies in patients with postmenopausal bleeding. **Study design:** Cross section controlled study. **Patients and Methods:** The study included three groups 15 patients each with postmenopausal bleeding diagnosed by endometrial biopsy as: atrophic endometrium, endometrial hyperplasia and endometrial carcinoma. Fasting serum leptin and adiponectin were measured by enzyme-linked immunosorbent assay. **Outcome measure:** Serum leptin and adiponectin levels in the three studied groups and the value of leptin / adiponectin ratio were investigated as a marker for endometrial pathologies. **Results:** Serum leptin level was significantly higher and serum adiponectin was significantly lower in patients with endometrial hyperplasia and endometrial carcinoma compared to patients with atrophic endometrium ($P<0.00$). Leptin / adiponectin ratio of >1.1 was a good test that indicated endometrial hyperplasia and endometrial carcinoma with an accuracy of 83.3% and 90% respectively. **Conclusions:** Serum leptin/adiponectin ratio may help in differentiation between atrophic and other endometrial pathologies in cases of inconclusive endometrial thickness and when general anesthesia is risky especially in obese, hypertensive patients. However, endometrial biopsy still remains the gold standard diagnosis for endometrial carcinoma.
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Kew words: Serum leptin / adiponectin ratio, postmenopausal bleeding, endometrial pathologies.

1. Introduction

The dictum postmenopausal bleeding (PMB) indicates malignancy until proved otherwise is still valid, and the histopathology examination of the endometrium still remains the gold standard diagnosis for endometrial pathology. However, 70% - 80% will have benign diagnosis so; dilatation and curettage (D&C) for all patients is still questioned **(Sousa *et al.*, 2001)**.

Usage of trans-vaginal ultrasound measurement of the endometrial thickness is introduced to reduce operative procedure, but a controversy still exists regarding the cutoff measure of the endometrium which necessitate D&C and there is considerable false negative and false positive rates in the diagnosis of endometrial carcinoma (EC) **(Philip *et al.*, 2004; Shadev, 2007)**.

Obesity is a well known risk factor for the development of EC with the level of risk related to the degree of obesity **(World Cancer Research, 2007)**. Leptin is a 16-kDa, 167 amino acids and adiponectin is a 30-kDa, 244 amino acids. Both adipokines are secreted by white adipose tissue with their receptors mRNA are expressed in the endometrium **(Viengchareun *et al.*, 2002; Petridou *et al.*, 2002a)**.

The effect of leptin on endometrial carcinogenesis is due to induction of cell growth and stimulation of its progression **(Koda *et al.*, 2007)** while adiponectin acts on suppression of cell proliferation in human carcinoma cells **(Petridou *et al.*, 2002b)**. High leptin levels and low adiponectin levels were positively associated with increased risk of endometrial cancer while high adiponectin levels were positively associated with reduced risk **(Cust *et al.*, 2007)**. The relations between obesity, adipokines levels and endometrial cancer have been observed by different authors **(Cymbaluk *et al.*, 2008; Ashizawa *et al.*, 2010)**. However, the value of serum leptin / adiponectin (L / A) ratio as marker of endometrial pathologies in patients with PMB is not yet settled.

2. Patients and methods:

This cross-section study was performed in the department of Obstetrics and Gynecology, Benha Faculty of Medicine, during the period from May 2011 to September 2012. The protocol of the thesis was approved by the local ethical committee

and consent was taken from every patient before enrolling in the study. Patients with PMB bleeding were subjected to full history and general, abdominal and pelvic examinations. The body mass index (weight in Kg / height in M^2) and the mean arterial pressure (1/3 of the systolic pressure + 2/3 of the diastolic pressure) were calculated. The patient was considered overweight if the BMI was 25-30, obese if > 30 and hypertensive if the MAP was > 90. Trans-vaginal ultrasound was done and endometrial biopsy taken under general anesthesia for histopathology examination. Three groups of patients each 15 cases with atrophic endometrium, endometrial hyperplasia and endometrial carcinoma were included in the study. A fasting blood sample was taken and serum separated for estimation serum leptin (ng/ml) and adiponectin (µg/ml) levels using specific enzyme-linked immunosorbent assay (ELISA) method, (immunospec, 7018 Owensmouth Ave, Suite 103, Canoga Park, CA 91303, USA).

Statistical design:

Results were analyzed using SPSS version 20. Data were expressed as mean ± standard deviation for quantitative data, the Fisher exact (F) test for analysis of contingency tables. The Receiver Operator Characteristic (ROC) curve was used to evaluate serum L / A ratio as a test for the differentiation between atrophic and hyperplastic and malignant endometrium. An area under the ROC curve from 0.9 – 1 represents an excellent test, from 0.8 – 0.9 a good test, from 0.7 – 0.8 a fair test, from 0.6 – 0.7 a poor test and from 0.5 – 0.6 a fail test. Validity of the test at a certain cutoff point was represented by the sensitivity, specificity, positive and negative predictive values and accuracy. Result was considered significant at a *P* value of ≤0.05.

3. Results:

Table 1 shows significant higher body mass index, mean arterial pressure, serum leptin level, leptin / adiponectin ratio, and significant lower serum adiponectin level in patients with endometrial hyperplasia and endometrial carcinoma compared to patients with atrophic endometrium (*P*<0.019-0.00).

Table 1: Demographic data and serum levels in the study groups

	Atrophic	Hyperplasia	Carcinoma	F	*P*
Age	60.1 ± 7.5	60.8 ± 6.6	61.10 ± 7.90	0.08	0.910
Parity	2.9 ± 1.2	2.5 ± 0.7	2.90 ± 1.0	0.84	0.430
BMI	24.0 ± 3.2	27.3 ± 3.8	28.10 ± 4.8	4.33	0.019
MAP	94.2 ± 6.1	111.3 ± 80	115.0 ± 10.0	27.56	0.001
Leptin	15.3 ± 7.4	24.7 ± 70	25.0 ± 4.46	27.15	0.00*
Adiponectin	24.4 ± 4.7	15.1 ± 3.4	16.5 ± 2.6	32.77	0.00*
L / A ratio	0.6 ± 0.16	1.51 ± 0.4	1.79 ± 0.5	40.70	0.00*

BMI: Body mass index; MAP: Mean arterial pressure; L/A: leptin/adiponectin; *highly significant

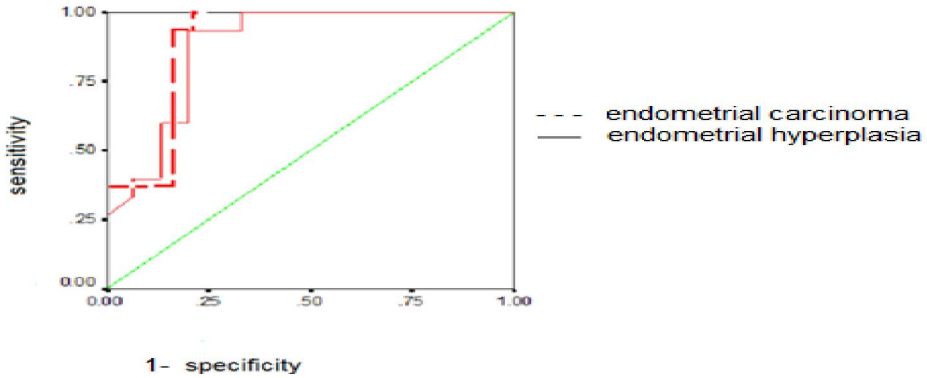

Figure (1) shows that serum leptin/adiponectin ratio was a good test for diagnosis of endometrial hyperplasia (AUC # 95% CI = 0.878) and endometrial carcinoma (AUC # 95% CI = 0.916).

Test Result Variables

	AUC	Std. Error	Asymptotic Sig	Asymptotic 95% CI	
				Lower bound	Upper bound
Hyperplasia	0.87	0.066	0.000	0.748	1.008
Carcinoma	0.91	0.057	0.000	0.804	1.027

AUC: area under curve; Std error: standard error; CI: Confidence interval

Table 2 shows significant positive correlation between serum leptin level and body mass index and mean arterial pressure (P<0.01–<0.001) and significant negative correlation between serum adiponectin level and body mass index (P<0.001)

Table 2: Correlation between serum leptin and serum adiponectin levels and BMI and MAP

	BMI		MAP	
	r	*p*	r	*P*
Leptin	+ve 0.38	0.01	+ve 0.41	0.001
Adiponectin	-ve 0.41	0.001	+ve 0.22	0.30

BMI: Body mass index; MAP: Mean arterial pressure

Table 3 shows that serum leptin / adiponectin ratio >1.1 was 83.3% and 90% accurate in the in the diagnosis of endometrial hyperplasia and endometrial carcinoma respectively.

Table 3: Performance of serum leptin / adiponectin ratio in the diagnosis of endometrial hyperplasia and endometrial carcinoma

Ratio	Hyperplasia		Sensitivity	Specificity	Predictive value		Accuracy
	+ve	-ve			+ve	-ve	
>1.1	12	2	80.0%	86.7%	85.7	81.3	83.3
≤1.1	3	13					
Ratio	Carcinoma		Sensitivity	Specificity	Predictive value		Accuracy
	+ve	-ve			+ve	-ve	
>1.1	14	2	93.3%	86.7%	87.5%	92.9%	90.0%
≤1.1	1	13					

4. Discussion:

Obesity is a risk factor for postmenopausal endometrial cancer. Elevated estrogen levels are thought to be a growth factor associated with this relationship, however, there is increasing evidences that the adipokines: leptin and adiponectin, produced in adipose tissue, impact several obesity-related cancers **(Ashizawa *et al.*, 2010)**.

In the present study, patients with endometrial hyperplasia and endometrial carcinoma were overweight and had significant higher BMI (P<0.019) compared to patients with atrophic endometrium. This result agrees with other studies that reported an association between elevated BMI and an increased risk of endometrial hyperplasia and endometrial carcinoma **(Reeves *et al.*, 2007; Viola *et al.*, 2008; Heller *et al.*, 2011)**. Excess body weight may influence cancer risk because of elevated levels of insulin-like growth factor 1, insulin, and sex steroid hormone especially estrogen which can promote the growth of cancer cells **(World Cancer Research, 2007).** Also, obesity has been described as a state of low grade chronic inflammation and that rise of pro-inflammatory response factors like tumor necrosis factor alpha, interleukin-6 and C-reactive protein can promote cancer cells **(Booth *et al.*, 2006)**.

In the present study patients with hyperplasia and carcinoma were hypertensive and had significant higher MAP (P<0.001) compared to patients with atrophic endometrium. This result agrees with that previously reported of increased risk of endometrial hyperplasia with aging, diabetes mellitus, hypertension and estrogen replacement therapy **(Nazari *et al.*, 2006)**.

In the present study patients with hyperplasia and cancer had significant higher serum leptin level compared to patients with atrophic endometrium (P<0.00), and there was a significant positive correlation between leptin level and BMI and MAP (P<0.01 – 0.001). This result agrees with that reported in other studies of the positive association between circulating leptin level, obesity and endometrial cancer **(Petridou *et al.*, 2002a; Cymbaluk *et al.*, 2008; Ospino *et al.*, 2010)**. Leptin receptors (Ob-R) mRNA are expressed in the endometrium and its carcinogenic effect is due to leptin-induced cell growth and invasiveness of cancer cells and the autocrine effect of leptin that stimulate endometrial cancer progression **(Koda *et al.*, 2007)**.

Sousa et al., (2001) found circulating leptin level was significantly higher in endometrial cancer patients than in normal control, however this association was not observed after BMI normalization and the authors reported that Ob-R1 and Ob-R6 are expressed in both cancer and non-cancer endometrium and that the abundance of Ob-R1 was similar in cancer and normal tissues, but levels of Ob-R6 were significantly decreased in malignant cells, suggesting that loss of Ob-R6 in endometrial cancer might contribute to malignant progression **(Yuan *et al.*, 2004)**. The significant positive correlation between serum leptin level and MAP reported in the present study was also observed by other authors who concluded that in

postmenopausal women increased leptin level may play an important role in the pathogenesis of hypertension independent of BMI **(Olszanecka *et al.*, 2010)**.

In the present study patients with endometrial hyperplasia and carcinoma had significant lower serum adiponectin level compared to patients with atrophic endometrium (P<0.00), and there was a significant negative correlation between adiponectin level and BMI (P<0.001) and no correlation was found with MAP. These results agree with other studies that found an inverse association between endometrial cancer risk and plasma adiponectin levels **(Petridou *et al.*, 2002b, Dal Maso *et al.*, 2004; Rzepka-Gorska *et al.*, 2008)** and that adiponectin level was negatively correlated with BMI **(Milewicz *et al.*, 2010)**.

In another study, significant negative correlation was found between adiponectin/ BMI and MAP pressure in pre-menopausal healthy asymptomatic but not in postmenopausal women. In the present study patients with hyperplasia and carcinoma had significant higher L/A ratio compared to patients with atrophic endometrium **(Kotani *et al.*, 2005)**. The ROC curve showed that a ratio of > 1.1 was 80% sensitive, 86.7% specific and 83.3% accurate in diagnosis of endometrial hyperplasia and 93.3%, 86.7% and 90% for diagnosis of endometrial carcinoma. This result was reported in a previous study that found significant higher L / A ratio to be independently associated with an increased risk of endometrial cancer development **(Ashizawa *et al.*, 2010)**.

Conclusions:

Serum leptin / adiponectin ratio may help in differentiation between atrophic and other endometrial pathologies in cases of inconclusive endometrial thickness and when general anesthesia is risky especially in obese, hypertensive patients. However, endometrial biopsy still remains the gold standard diagnosis for endometrial carcinoma.

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