Adiponectin to leptin index as a marker of endometrial cancer in postmenopausal women with abnormal vaginal bleeding: an observational study

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Abstract

OBJECTIVES: To evaluate the correlation between endometrial cancer and adiponectin plasma concentration, leptin plasma concentration as well as adiponectin to leptin index in the population of postmenopausal women with abnormal vaginal bleeding.
DESIGN: An observational study
SETTING: Department of Gynecology and Obstetrics, Specialist Teaching Hospital in Tychy, Poland. Population. 99 women between 47 and 88 years old, in postmenopausal state.
METHODS. The cases (54 women) were females hospitalized due to postmenopausal vaginal bleeding in whom dilation and curettage (D&C) was performed and endometrial intraepithelial neoplasia (EIN) was diagnosed in anathomopathology. Hysterectomy was then performed in all cases and the endometrial cancer diagnosis was confirmed. The controls (45 women) consists of females with no postmenopausal uterine bleeding in whom endometrial thickness in transvaginal ultrasound was greater than 5 mm. D&C was than performed and no endometrial neoplasia was detected in any of the subjects. Adiponectin and leptin plasma concentration was measured in both groups.
Mein outcome measures. The area under the curve, sensitivity, specificity and cutoffs for adiponectin, leptin and adiponectin to leptin index.
RESULTS: Adiponectin, leptin and adiponectin to leptin index were statistically correlated with the risk of endometrial cancer. At the suggested cutoffs, corresponding to the highest accuracy (minimal false-negative and false-positive results), adiponectin to leptin index resulted in the highest sensitivity and specificity compared to adiponectin and leptin alone.
CONCLUSIONS: Adiponectin to leptin index due to the highest sensitivity and specificity may be used as a marker of endometrial cancer in postmenopausal women with abnormal vaginal bleeding.

ORIGINAL ARTICLE

INTRODUCTION

Endometrial carcinoma is the fourth most frequent cancer in women and occurs typically in postmenopausal period (Tassi *et al*. 2008). Two types of endometrial cancer were identified. Type I (endometrioid) endometrial carcinoma accounts for approximately 80% of all endometrial cancers; this type can be seen in both premenopausal and perimenopausal women and is predominantly preceded by atypical hyperplasia and tends to be estrogen dependant. Type II (nonendometrioid) develops usually in postmenopausal females and is mainly serous papillary or clear cell carcinoma; it tends to be high grade and might be preceded by endometrial intraepithelial carcinoma and is usually not estrogen dependant (Tassi *et al*. 2008; Ellis & Ghaem-Maghami 2010).

More than 90% of postmenopausal patients with endometrial carcinoma have vaginal bleeding. On the other hand, more than 90% of postmenopausal and more than 98% of pre- and perimenopausal women with abnormal bleeding may have a benign underlying cause (Dimitraki *et al*. 2011). It raises the question what would be the best method of detecting the women with the high risk of endometrial carcinoma and clinical evaluation of women with postmenopausal bleeding (PMB). So far transvaginal ultrasound (TVUS) and histological evaluation (pipelle endometrial biopsy or dilation and curettage) are the gold standard and have the similar sensitivities for detecting endometrial carcinoma when an endometrial thickness of greater than 5 mm is considered abnormal and for endometrial biopsy when adequate tissue is obtained (Dimitraki et al. 2011; van Hanegem *et al*. 2011; Smith-Bindman *et al*. 2004). However, there are still controversies regarding the effectiveness and cost-effectiveness of both methods. There is a need for additional markers that could be helpful in detecting the risk groups and targeting them for further diagnostic procedures and management.

A few risk factors and possible molecular and genetic markers of endometrial cancer have been identified. Obesity, polycystic ovarian disease, diabetes, hypertension, nulliparity, tamoxifen use, Hereditary Non-Polyposis Colorectal Cancer and late menopause are the most known risk factors. PTEN gene mutation resulting in the deregulation of the mTOR (mammalian target of rapamycin) pathway, PTEN inactivation, FOXO1 transcription factor, elevated insulin like growth factor 1 (IGF-1), β-catenin level, E-catherin expression, mutation in K-ras gene and overexpression of p53, mammaglobin B, HER-2/neu gene and pp125 focal adhesion kinase (FAK) expression have been reported as possible markers and targets for new therapeutics for endometrial carcinoma (Tassi *et al*. 2008; Ellis & Ghaem-Maghami 2010; Smith-Bindman *et al*. 2004; Tong *et al*. 2009; Gabriel *et al*. 2009; Markova *et al*. 2010). However, none of them did reach the specificity and sensitivity in detecting the malignancy as Ca125, HE4 and ROMA algorithm in case of ovarian cancer (Van Gorp *et al*. 2011; Montagnana *et al*.2011).

Recently, a potential role of adipocytokines like adiponectin and leptin as well as other angiogenesis regulators (e.g. vascular endothelial growth factor) in detecting endometrial cancer has been suggested (Lasalandra *et al*. 2010; Matsubara *et al*. 2002). Adiponectin induces antiangiogenesis and prevents new blood vessel growth. It has also anti-inflammatory, anticancer and insulin-sensitizing effects. Plasma adiponectin concentrations were found to be decreased in patients with obesity, non-insulin-dependent diabetes mellitus, insulin resistance, dyslipidemia and cardiovascular disease (Matsubara *et al*. 2002). In a few studies adiponectin levels were inversely and independently associated with endometrial cancer (Montagnana *et al*.2011; Chovanec *et al*. 2006; Petridou *et al*. 2003; Kelesidis *et al*. 2006; Soliman *et al*. 2006; Cust *et al*. 2007; Dal Maso *et al*. 2004; Cong *et al*. 2007). In contrast, Chovance et al. in their preliminary study revealed no correlation between leptin and adiponectin polymorphisms and endometrial cancer (Chovanec *et al*. 2006).

Leptin, the obese (ob) gene product, is believed to be a lipostatic hormone which concentration is highly correlated with body-fat storage. Serum leptin concentration was shown to be increased (hyperleptinemia due to leptine resistance) in humans with obesity, insulin resistance and dyslipidaemia. Leptin causes an oxidative stress in endothelial cells via multiple signal-transduction pathways including activation of COX- 2 and other kinases (JAK2/STAT3-, MAPK/ERK-, and PI3K/AKT). Thus, hyperleptimenia may be a critical factor of endometrial carcinogenesis in obesity (Matsubara *et al*. 2002; Gao *et al*. 2009; Petridou *et al*. 2002).

Plasma leptin concentration was showed to be positively and independently correlated with the risk of endometrial cancer (Petridou *et al*. 2002). However, Petridou et al, revealed that this correlated was not significant after adjusting for BMI. Thus it cannot be concluded, whether leptin elevation, as a consequence of obesity, plays a role in endometrial carcinogenesis or whether it is a simple correlate of obesity (Petridou *et al*. 2002).

The studies on correlation between endometrial cancer and both adiponectin and leptin concentration are lacking. In the study by Matsubara et al. a significant inverse relationship between plasma adiponectin and leptin concentrations that was independent of age, blood urea nitrogen, blood pressure, body composition, lipid and insulin resistance was described in healthy subjects (Matsubara *et al*. 2002). Further research is needed to determine the correlation of those adipocytokines in case of endometrial cancer.

MATERIAL AND METHODS

Patients

The research was conducted between January 2009 and December 2010. 123 women aged 47–88 years old in

postmenopausal status defined as a lack of having menstrual periods confirmed after 12 consecutive months of amenorrhea with no obvious pathologic cause and FHS levels >30 IU/ml were eligible for the study (North American Menopause Society 2010). Females with thyroid diseases (struma nodosa; abnormal levels of TSH, fT3 and fT4), endometriosis, uterine myomas, history of breast diseases, ovarian tumors and pelvic masses seen in transvaginal ultrasound scans, renal failure (serum creatinine >159 mmol/l or blood urea nitrogen >10.7 mmol/l), chronic liver dysfunctions (elevated total bilirubin, gamma glutamyl transpeptidase, aspartate transaminase, alanine transaminase or alkaline phosphatase), severe or chronic inflammatory diseases, diabetes mellitus (fasting blood glucose >7.0 mmol/l or blood glucose >11.1 mmol/l 2 h after 75 g oral glucose loading), untreated endocrine diseases and presence of cancers (except endometrial cancer in investigated group) were excluded from the study. Finally, 99 women were included in the study, 54 to the investigated group and 45 to controls.

The control group consists of females who were hospitalized due to pelvic organ prolaps or stress urinary incontinence with no postmenopausal uterine bleeding in whom endometrial thickness in transvaginal ultrasound was greater than 5 mm (Dimitraki et al 2011; van Hanegem *et al.* 2011; Smith-Bindman *et al.* 2004). Dilation and curettage (D&C) was than performed in each patients. No endometrial neoplasia was detected in any of the subjects.

The investigated group (cases) was females hospitalized due to postmenopausal vaginal bleeding in whom D&C was performed and endometrial intraepithelial neoplasia (EIN) was diagnosed in anathomopathology. Hysterectomy was then performed in all cases and the endometrial cancer diagnosis was confirmed in histological examination of hysterectomy specimens.

Serum assay

Fasting morning blood sample were collected from each patients upon admission for measurements of adiponectin and leptin plasma levels as well as levels of FHS,TSH, fT3, fT4 and other biochemical parameters. Plasma adiponectin concentrations were measured using a commercial human adiponectin ELISA kit (B-Bridge International Inc., Sunnyvale, USA) with a detection limit, and intra- and interassay coefficients of variation of 7.0 ng/ml, 7.0% and 8.2%, respectively. Plasma leptin concentrations were measured using a commercial human leptin radioimmunoassay kit (Linco Research, Missouri, USA) with a detection limit, and intra- and interassay coefficients of variation of 0.5 ng/ml, 4.6% and 5.0%, respectively.

As leptin levels in serum depends on body mass index (BMI) (van Hanegem *et al.* 2011) cases and controls were divided into 3 subgroups based on BMI: normal weight (BMI<25), overweight (BMI=25–35) and obese (BMI>35). The subgroups were then compared in between.

Statistical analysis

The results were analyzed in Statistica 9.0 pl (StatSoft, Krakow, Poland). The mean age of the patients was compared using Student's t-test, and categorical variables were compared with the chi-square test. Adiponectin and leptin levels as well as adiponectin to leptin index (A/L) were compared using the Mann–Whitney U test. Receiver operator characteristic (ROC) curves were constructed, and the area under the curve (ROC-AUC) with a 95% confidence interval was calculated. Sensitivity and specificity were calculated in normal weight, overweight and obese subgroups of patients pre- and post-menopausal women separately and independently of menopausal status. The method described by DeLong et al. was used for the calculation of the difference between two ROC-AUCs (DeLong *et al.* 1988). A cutoff points for adiponectin, leptin and A/L, that provided the best accuracy (minimal false-negative and false positive results), was determined. For all statistical comparisons, a p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of respondents was 58.8 ±13.2 years. There were no statistical differences between cases and controls in age, mean BMI distribution, number of smoking patients and parity (Table 1). However, the number of obese patient was higher in cases compared to controls.

Among 54 cases endometrial cancer was confirmed postoperatively, based on the anatomopathological

Tab. 1. General characteristic of the studied population.

Variable	Controls (n=45)	Cases (n=54)	*p*-value*
Age mean±SD, range, yr	56.6±14.82 (47–88)	60.6±11.56 (50–84)	NS
BMI mean±SD, range, kg/m^2	26.1±5.11 (17.5–38.7)	30.5±5.81 (20.5–48.2)	NS
BMI categories, n (%)			
Normal weight (BMI <25 kg/m^2)	20 (44.4)	9 (16.7)	0.004
Overweight (BMI, 25-30 kg/m^2)	13 (28.9)	16 (29.6)	
Obese (BMI >30 kg/m^2)	12 (26.7)	29 (53.7)	
Smoking, n (%)	16 (35.6)	20 (37.0)	
Parity (median, upper and lower quartile)	2 (2-3)	2 (2-3)	NS

* Chi^2 test

examination of the hysterectomy specimen. Histological type of endometrial cancer diagnosed in cases presents Table 2.

The mean plasma adiponectin concentration and A/L was higher in controls compared to females with endometrial cancer. In contrast, the mean plasma leptin levels were statistically higher in cases compared to controls (Table 3).

The statistical analysis revealed that all markers (adiponectin, leptin and A/L) were statistically correlated the risk of endometrial cancer. Adiponectin and adiponectin to leptin index were positively, whereas leptin was negatively correlated with that risk – Spearman correlation coefficient: r=0.47 (p=0.000001); r=0.37 (p=0.0002) and r=–0.23 (p=0.03), respectively. Furthermore, the analysis showed that all markers were not correlated with age; however, all were statistically correlated with BMI (Spearman correlation coefficient: r=–0.37, p=0.0001 for adiponectin; r=0.64, p=0.0000001 for leptin; r=–0.66, p=0000001 for A/L). For that reason ROC-AUC and cutoffs were calculated for three BMI groups (normal weight, overweight and obese) separately.

The ROC-AUC of adiponectin was not significantly different from that of adiponectin to leptin index for all endometrial cancer patients compared with healthy subjects (Table 4, Figure 1). The ROC-AUC of leptin was lover compared to both adiponectin and adiponectin to leptin index. Pairwise comparison of ROC-AUCs showed that only the difference between leptin and adiponectin as well as leptin and A/L was significant. Overall, adiponectin to leptin index did not perform significantly better than adiponectin alone but better that leptin alone. However, at the suggested cutoffs, corresponding to the highest accuracy (minimal false-negative and false-positive results), A/L resulted in the highest sensitivity and specificity compared to adiponectin and leptin alone. The positive and negative predictive values (PPV and NPV) for adiponectin to leptin index were 63.7% and 88.2%, respectively. PPV and NPV for adiponectin were 81.4% and 65.5%; for leptin – 71.1% and 55.9%, respectively.

The analysis of AUC-ROCs in BMI subgroups revealed no statistically significant differences between adiponectin, leptin and A/L, except for obese patient (Table 4, Figure 1). In normal weight patient the leptin concentration had the highest sensitivity and specificity compared to other two markers. However, in case of overweight and obese females adiponectin to leptin

Tab. 2. Histological type of endometrial cancer in cases.

Type of cancer	Number of cases	%
Endometrial adenocarcinoma	37	58.4
Endometrial adenosquamous carcinoma	1	1.8
Non endometrioid Papillary serous carcinoma	1	1.8
Carcinoma adenosquamosum	1	1.8
Adenoacanthoma	11	20.6
Adenocarcinoma partim clarocellulare	2	3.6
Adenocarcinoma clarocellulare	1	1.8
Adenocarcinoma necroticans	1	1.8
Adenosquamousu carcinoma	1	1.8
Small cell carcinoma	1	1.8
Mesonephroid carcinoma [Clear cell]	1	1.8
Total	54	100
Grading		
G1	22	40.7
G2	26	48.2
G3	6	11.1
Total	54	100.0

Tab. 3. Adiponectin, leptin plasma levels and adiponectin to leptin index in the studied population.

Variable	cases				controls				*p*-value*
	mean	median	range	SD	mean	median	range	SD	
Adiponectin (ug/ml)	12.17	11.29	4.49–29.07	5.63	18.06	17.21	6.88–45.30	7.00	0.00001
Normal weight	13.76	11.98	7.96–21.42	4.32	20.23	18.99	8.92–45.39	8.20	0.01
Overweight	13.35	11.55	5.10–26.62	6.01	17.12	15.81	6.88–28.56	6.54	0.1
Obese	11.02	9.28	4.49–29.07	5.68	15.07	16.32	8.92–20.40	3.21	0.004
Leptin (ng/ml)	19.26	19.50	3.90–46.00	10.49	14.92	13.35	1.40–42.00	9.68	0.03
Normal weight	10.50	8.15	5.50–26.70	6.87	8.31	7.65	1.40–18.00	4.85	0.52
Overweight	15.94	15.40	6.20–29.90	6.72	15.70	15.60	9.30–24,20	4.86	0.96
Obese	23.50	23.00	3.90–46.00	11.03	26.02	22.00	13.80–42.00	10,29	0.77
Adiponectin to leptin ratio	0.89	0.67	0.16–3.01	0.67	2.34	1.16	0.28–13.66	2.94	0.00002

* Man-Whitman U test

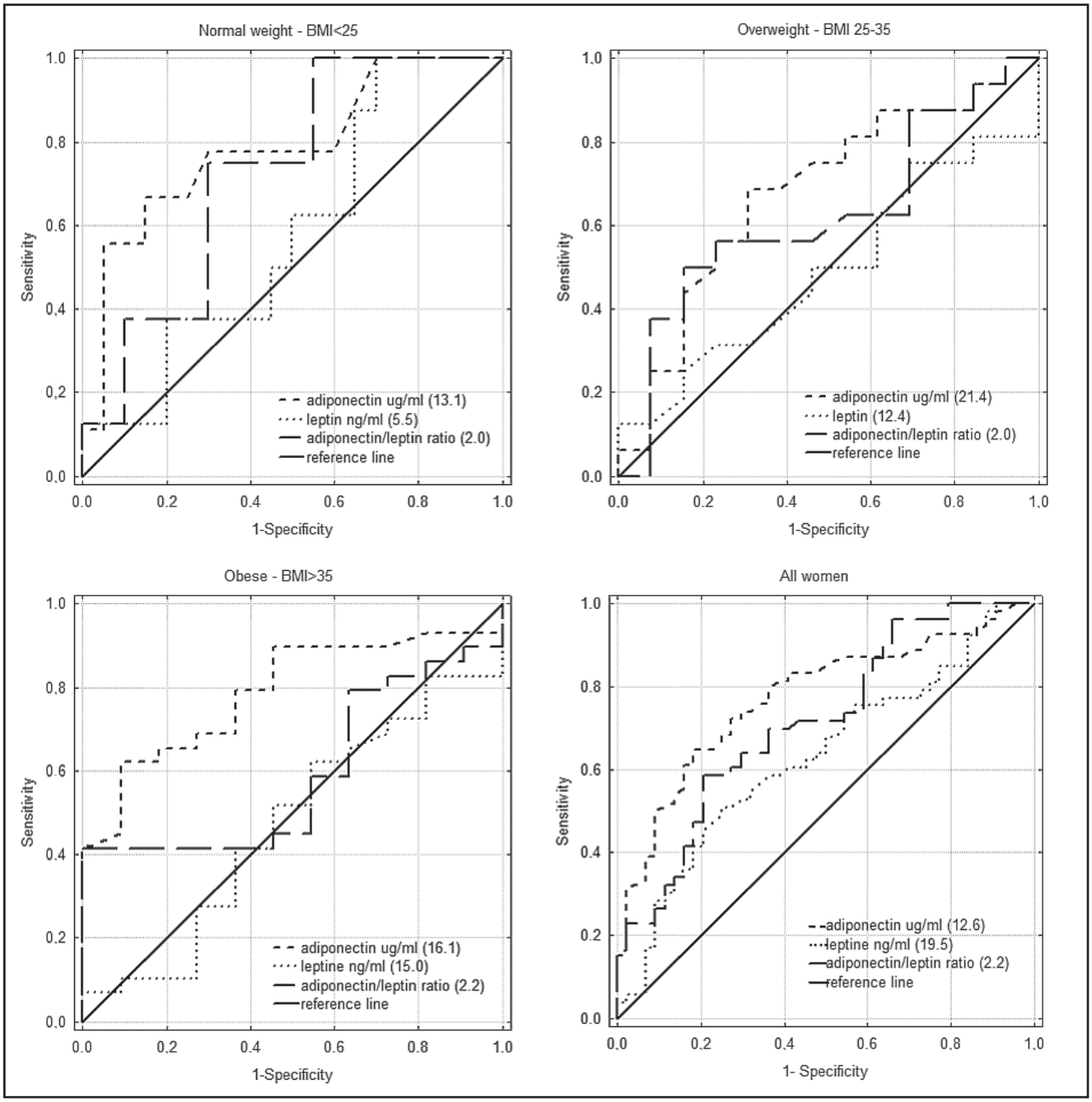

Fig.1. ROC curves for adiponectin, leptin and adiponectin to leptin index among all studied women and subgroups according to body mass index (endometrial cancer patients vs healthy females).

index showed the highest sensitivity and specificity at the suggested cutoffs compared to adiponectin and leptin concentration alone.

DISCUSSION

We believe that this is one of few studies on the correlation of both adiponectin and leptin with the risk of endometrial cancer. We aimed to determine the specificity and sensitivity of adiponectin, leptin and adiponectin to leptin index as markers of endometrial cancer in postmenopausal women. Furthermore we established cutoffs, sensitivity and specificity for adiponectin, leptin and adiponectin to leptin index in normal weight, overweight and obese women.

A few recent studies revealed that adiponectin was inversely related with the risk of endometrial cancer, especially among women younger than 65 years (Petridou *et al*. 2003; Kelesidis *et al*. 2006; Soliman *et al*. 2006; Cust *et al*. 2007; Dal Maso *et al*. 2004; Cong *et al*. 2007). Furthermore, Petridou et al., Miyoshi et al. and Mantzoros et al. showed that the inverse relation of adiponectin with risk of endometrial cancer was independent of possible effects of other cytokines: IGF-I,

Tab. 4. Comparison of ROC–AUCs, sensitivity and specificity for adiponectin, leptin and adiponectin to leptin index among studied patients.

Patients	Marker	ROC-AUC (95% CI)	Pairwise comparison of ROC-AUV[a]			Suggested cutoff[b]		
			A vs A/L	A vs L	L vs A/L	Cutoff	Sensitivity (%)	Specificity(%)
All	Adiponectin	0.77 (0.68–0.87)				12.6	64.8	18.2
	Leptin	0.63 (0.52–0.74)	*p*=0.21	*p*=0.04	*p*=0.006	19.5	50.9	25.0
	A/L	0.71 (0.62–0.82				2.2	92.0	65.9
Normal weight	Adiponectin	0.79 (0.60–0.97)				13.1	66.7	15.0
	Leptin	0.58 (0.36–0.81)	*p*=0.67	*p*=0.21	*p*=0.06	5.5	100.0	70.0
	A/L	0.73 (0.53–0.92)				2.0	75.0	30.0
Over-weight	Adiponectin	0.68 (0.48–0.88)				21.4	87.5	61.5
	Leptin	0.49 (0.28–0.71)	*p*=0.46	*p*=0.20	*p*=0.19	12.4	75.0	69.2
	A/L	0.62 (0.41–0.83)				2.0	100.0	92.3
Obese	Adiponectin	0.79 (0.64–0.93)				16.1	89.7	54.5
	Leptin	0.50 (0.27–0.67)	*p*=0.02	*p*=0.01	*p*=0.06	15.0	82.8	88.9
	A/L	0.59 (0.41–0.77)				2.2	99.7	90.1

Abbreviations: A – adiponectin; L – leptin; A/L – adiponectin to leptin index; ROC-AUC – receiver operator characteristic – area under the curve; CI – confidence interval; [a] – Differences in ROC–AUCs were calculated by using the method as described by DeLong et al, 1988; [b] – Cutoff value corresponding to the highest accuracy (minimal false-negative and false-positive results).

IGF-II, IGFBP-3, leptin, as well as BMI and other known risk factors (Kelesidis *et al*. 2006). The possible mechanism of adiponectin action might be the sensitizing effect of low adiponectin on endometrium to circulating insulin and other IGFs, potentiated by circulating estrogens. Additionally, the inhibitory effects of adiponectin are associated with the reduction of different pro-growth regulators of cell cycle and signaling proteins (Petridou *et al*. 2003; Cong *et al*. 2007).

Serum leptin concentration was showed to be positively correlated with the risk of endometrial cancer in a few studies (Gao *et al*. 2009; Petridou *el al*. 2002). However, some authors revealed no statistically significant differences in leptin levels between healthy subjects and endometrial cancer women when normalized by body mass index (Petridou *el al*. 2002; Yuan *et al*. 2004). This might be due to the tissue expression patterns of various leptin receptor isoforms and the complex signal transduction pathways what may influence the biological outcomes of leptin action (Yuan *et al*. 2004).

In our study adiponectin and adiponectin to leptin index were positively and leptin negatively correlated with the risk of endometrial cancer.

Similarly to other studies, the mean adiponectin level in endometrial cancer women was lover compared to controls (Kelesidis *et al*. 2006; Soliman *et al*. 2006). As in paper by Cust at al. in our study the difference was still significant in case of normal and obese women but not in overweight ones (Cust *et al*. 2007). Additionally, in contrast to other research (Lasalandra *et al*. 2010; Petridou *et al*. 2003; Kelesidis *et al*. 2006; Soliman *et al*. 2006; Cust *et al*. 2007; Dal Maso *et al*. 2004; Cong *et al*. 2007), the adiponectin concentration was negatively correlated with BMI.

In studies by Petridou et al., Yuan at al., and Cumbaluk et al. plasma leptin was significantly higher in endometrial cancer women (Petridou *et al*. 2002; Yuan *et al*. 2004) and in all BMI subgroups (Cymbaluk *et al*. 2008). In our study we did not show the significant differences neither in all women nor in BMI subgroups. However, similarly to other authors (Petridou *et al*. 2002; Yuan *et al*. 2004), we revealed the correlation between the leptin concentration and BMI.

Our study has also some limitations. Firstly, the study population is relatively small therefore the results should be interpreted with caution. Secondly, we did not include in the study women in reproductive age – the results cannot be extrapolated to premenopausal females. Thirdly, we did not assess adiponectin and leptin serum levels in cases after the surgical operation, so we cannot predict if the concentration of those cytokines changes postoperatively and thus if they may be useful in monitoring the effect of endometrial cancer treatment. Despite the promising results of our paper, further multicentre studies are needed to establish the role of adiponectin, leptin and adiponectin to leptin index in identification endometrial cancer risk groups in postmenopausal women with abnormal endometrial thickness or vaginal bleeding.

CONCLUSIONS

Adiponectin to leptin index due to the highest sensitivity and specificity compared to adiponectin and leptin alone at the suggested cutoffs, may be used as a marker of endometrial cancer, especially in case of overweight women in postmenopausal age with abnormal vaginal bleeding.

Disclosure of interests

The authors declare that there are no conflicts of interest.

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