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Visfatin, a potential biomarker and prognostic factor for endometrial cancer

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HIGHLIGHTS

- Visfatin, a newly discovered adipocytokine, may be a potential serum biomarker for EC and indicate high risk for EC.
- Visfatin is a potential prognostic factor for EC, involving in EC progression.
- Visfatin may be a novel potential therapy target for EC patients.

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ABSTRACT

Objective. Visfatin, a newly discovered adipocytokine, is thought to play a role in the pathogenesis of metabolic-syndrome-related cancers. The aim of this study was to assess the clinical significance of serum levels and tissue expression of visfatin in relation to endometrial cancer (EC).

Methods. A total of 234 EC patients were included in this study. Serum visfatin, metabolic and anthropometric parameters were measured in EC patients and controls. Serum visfatin levels were detected using ELISA. Tissue expression of visfatin was analyzed using immunohistochemistry in tissue microarrays. The correlation between clinicopathological variables and visfatin in EC tissues and the prognostic value of visfatin for overall survival was evaluated.

Results. Serum levels of visfatin were significantly higher in EC patients than in controls ($P<0.05$). In univariate and multivariate logistic regression models, a positive association between EC and serum visfatin, BMI, waist-to-hip ratio, diabetes, and hypertension was evident ($P<0.05$). Visfatin expression was significantly higher in EC tissue than in normal endometrial tissue ($P=0.001$). Moreover, serum visfatin levels were significantly positively correlated with tissue expression of visfatin in EC patients ($P<0.05$). High visfatin expression in EC tissues was significantly associated with advanced FIGO stage ($P=0.016$) and myometrial invasion $\geq 1/2$ ($P=0.023$). The overall survival rate of EC patients was significantly higher in the group with negative visfatin expression than with positive visfatin expression ($P=0.035$).

Conclusions. Visfatin is a potential serum biomarker and prognostic factor for EC that may indicate high risk for EC and EC progression. It may also be a novel potential therapeutic target for EC.

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Introduction

Endometrial carcinoma (EC) is one of the most common gynecologic malignancies in developed countries. During 2012, an estimated 47,130 new cases were diagnosed and 8010 deaths were attributed to EC in the United States [1]. The incidence rate of EC is increasing at a surprisingly rapid rate, both in the West and in China. Nevertheless, the exact mechanism of EC pathogenesis remains unclear. Therefore, it is critical to identify key pathogenesis factors and therapeutic targets for EC.

Metabolic syndrome (MS) comprises a group of risk factors including obesity, hypertension, insulin resistance, diabetes, and dyslipidemia that increase the risk of developing multiple types of cancer, particularly EC [2]. The physiopathological mechanism that links MS and EC is mostly related to abdominal obesity. Indeed, increasing body-mass index (BMI) and obesity were observed in many studies to be strongly associated with EC incidence and death from EC [3]. The most important characteristic of abdominal obesity is excess white adipose tissue. White

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adipose tissue is a complex endocrine organ that secretes a variety of adipocytokines including adiponectin, leptin, resistin, and visfatin [4] that play important roles in key aspects of metabolism, such as insulin resistance, fatty acid oxidation, inflammation, and immunity [5]. Recently, adipocytokines produced by adipose tissue have been the subject of intense investigation as novel risk markers for cancer, particularly those for which strong association between obesity and cancer risk exists: breast cancer [6], colorectal cancer [7], and EC [8].

The adipocytokine visfatin, also known as NAMPT/pre-B-cell-enhancing factor, exhibits nicotinamide phosphoribosyltransferase (NAMPT) activity and has been linked to several inflammatory disease states and cancer. Additionally, visfatin regulates growth, apoptosis, and angiogenesis in mammalian cells [9]. Notably, Fukuhara et al. also reported it as an insulin-mimetic adipokine [10]. These diverse roles suggest that visfatin may be an important component in physiological and disease states, especially in MS-related cancers. Recent studies demonstrated that high serum levels and tissue expression of visfatin were correlated with various cancers including breast cancer [6], colorectal cancer [7], prostate cancer [11], and gastric cancer [12]. Thus, visfatin may be an obesity-induced adipoctyokine involved in the development of MS-related cancers.

Although accumulating evidence suggests that visfatin may play important roles in multiple cancer types, there is no study, to our knowledge, on visfatin at the serum and tissue levels in EC. In this study, we examined the involvement of visfatin in EC and determined the correlation of visfatin expression with the clinicopathologic features of EC patients.

Materials and methods

Patient samples

This nested case–control study was conducted at Tianjin Medical University General Hospital, with recruitment taking place between 2003 and 2012. Patients were identified among women with a first diagnosis of histologically confirmed EC, none of whom had undergone radiotherapy or chemotherapy prior to surgery. A total of 234 patients were approached and all (100%) agreed to participate. Controls were selected among women who presented for routine examination in the Department of Regular Physical Examination Center or for uterine prolapse, cystocele, or urethrocele. None had a family history of cancer, and all were age-, time-, and nationality-matched to the patients. The study protocol was approved by the Ethics Committee of Tianjin Medical University General Hospital, and informed consent was obtained from each patient enrolled in the study.

From our study population, serum was collected in 120 cases and tissue samples in 164 cases, with both serum and tissue samples collected in 50 of the 234 cases. The remaining samples collected from the 234 cases were used in other studies [13,14]. Table 1 shows the basic characteristics of patients from whom only tissue was collected (tissue group, n = 114), from whom only serum was collected (serum group, n = 70), and from whom both tissue and serum were collected (overlap group, n = 50).

Clinicopathologic information

The clinicopathologic features of each case were recorded by two researchers independently, and the mean of each measurement was obtained. Height, weight, waist circumference, abdominal circumference, and hip circumference were measured using standard protocols. Using these measures, waist-to-hip ratio and BMI [weight (kg)/height^2 (m^2)] were calculated. Information on diabetes, hypertension, and family history of cancer was collected from each subject.

Serum collection

Serum was collected between 2003 and 2012 from 120 patients with EC and 120 age-, time-, and nationality-matched controls. One 5-mL blood specimen per patient was collected early in the morning after 6 h of fasting and prior to surgery, or the day of regular examination. The collected samples were centrifuged, and then serum was separated and stored at −80 °C. Serum samples collected before 2010 were used for other studies [13,14].

Table 1
Basic characteristics of the three groups of endometrial cancer patients in this study.

Variables	n = 114 (Tissue)	n = 70 (Serum)	n = 50 (Overlap)	χ^2	*P*
Age at diagnosis (years)					
<50	20 (17.54)	12 (17.14)	10 (20.00)	0.186	0.911
≥50	94 (82.46)	58 (82.86)	40 (80.00)		
Diabetes					
Yes	36 (31.58)	13 (18.57)	11 (22.00)	4.291	0.117
No	78 (68. 42)	57 (81.43)	39 (88.00)		
Hypertension					
Yes	36 (31.58)	30 (42.86)	16 (32.00)	2.682	0.262
No	78 (68. 42)	40 (57.14)	34 (68.00)		
BMI (kg/m^2)					
≤24	40 (35.09)	18 (25.71)	16 (32.00)	1.766	0.413
>24	74 (64.91)	52 (74.29)	34 (68.00)		
Histologic subtype					
Endometrioid	106 (92.98)	68 (97.14)	47 (94.00)	1.455	0.483
Nonendometrioid	8 (7.02)	2 (2.86)	3 (6.00)		
Histopathologic grade					
G1	49 (46.23)	26 (38.24)	22 (46.81)	5.125	0.275
G2	42 (39.62)	37 (54.41)	18 (38.30)		
G3	15 (14.15)	5 (7.35)	7 (14.89)		
Myometrial invasion					
<1/2	76 (66.67)	66 (94.28)	42 (82.00)	20.780	<**0.001***
≥1/2	38 (33.33)	4 (5.71)	8 (18.00)		
FIGO stage					
I–II	92 (80.70)	62 (88.57)	44 (88.00)	2.623	0.269
III–IV	22 (19.30)	8 (11.43)	6 (12.00)		
Lymph node metastasis					
Yes	16 (14.04)	6 (8.57)	4 (8.00)	1.934	0.380
No	98 (85.96)	64 (91.43)	46 (92.00)		

The data is presented as number of cases (percentage of cases).
* means P<0.05.

Tissue collection

Endometrial tissue samples were collected between 2003 and 2012 from 164 patients with EC, 24 patients with hyperplastic endometrium (HE), 25 patients with atypical hyperplastic endometrium (AHE), and 86 patients with normal proliferative or secretory endometrium (NE). The tissues were collected from hysterectomy specimens. The patients without EC in our study were admitted to our hospital for uterine prolapse, cystocele, or urethrocele. The histological type and grade of the primary tumors was determined by two independent pathologists based on a modified WHO classification system, whereas EC staging was performed based on a modified 2009 FIGO staging system [15].

Serum visfatin detection

Serum visfatin levels were measured using an ELISA kit according to the manufacturer's protocol (R&D, Inc., California, USA). The assay had a sensitivity of 0.1 ng/mL, with an intra-assay coefficient of variation of 5.2% and an interassay coefficient of variation of 5.8%. Experimental results were expressed as the mean ± SD of three independent experiments for each sample.

Tissue microarray

All tissues for tissue microarray were obtained from formalin-fixed, paraffin-embedded tissue blocks. All cases were histopathologically re-evaluated and tumor content verified in hematoxylin–eosin-stained slides. Representative areas of tumor and normal tissue were selected to be cored. The tissue microarray was designed and constructed using

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