Clinical significance of serum adipokine visfatin/eNampt in relation to prostate cancer detection and aggressiveness

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Background
Prostate cancer is a common malignancy ranked as the second most common cause of cancer and the fifth cause of cancer-related mortality worldwide. The association between obesity and prostate cancer remains poorly understood, but evidence suggests that obesity may adversely affect the risk of developing high-grade disease. Adipokines may contribute toward the molecular basis for a link between obesity and prostate cancer. Several studies have shown the role of visfatin in different cancers including astrocytomas, myeloma, and male oral squamous cell; gastric, endometrial, hepatocellular, and colorectal carcinomas; and invasive breast cancer.

Objective
In the present study, we attempted to investigate whether a high serum level of visfatin is a good biomarker associated with prostate cancer, especially high-grade cancer, and in obese patients; then, it could be used as a biomarker for the detection of prostate cancer and to determine its aggressiveness.

Participants and method
The present study included 89 individuals divided as follows: 15 age-matched volunteers, control group (group I), 36 patients diagnosed with benign prostatic hyperplasia (BPH group) (group II), and 38 patients diagnosed with prostate cancer (PC group) (group III).

Results
There was a statistically significant increase in serum visfatin level in PC patients (group III) compared with both the controls (group I) and patients with BPH (group II) ($P < 0.001$, $P < 0.001$, respectively). In PC patients, the median value of serum visfatin was 55.36 ng/ml (44.32–94.02), whereas it was 12.06 ng/ml (10.36–17.74) in the BPH group and 14.89 ng/ml (10.68–18.62) in the control group. BMI, visfatin, and prostatic-specific antigen were found to be the major significant determinants of the tumor grade (Gleason score) of PC (with a 95% confidence interval 0.096–0.233, $P < 0.001$; 0.083–0.016, $P = 0.005$; and 0.001–0.019, $P = 0.033$, respectively).

Conclusion
In this study, we found a significant positive association between serum visfatin and PC, especially in obese individuals, and we suggest that visfatin could be used as a new promising biomarker for PC; further investigations are warranted to confirm its role in the diagnosis of PC and to assess its aggressiveness.

Keywords:
BMI, Gleason score, prostate cancer, serum visfatin

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Introduction

Prostate cancer (PC) is a common malignancy ranked as the second most common cause of cancer and the fifth cause of cancer-related mortality worldwide [1]. The oldest reported case of PC was discovered in a 2000-year-old Egyptian mummy [2]. PC rates vary by geographic location, with the western countries having the highest incidence rates [3]. Obesity shares the same geographic distribution as PC [4]. The relationship between PC and obesity has been investigated extensively in the literature recently. The epidemiologic coexistence of both diseases was studied in several epidemiologic reports, with contradictory results [5,6].

Recent studies obviously showed a clear association of obesity with aggressiveness of PC [7–9]. A multicenter study examined the pathologic variables in obese patients with PC. Among 3162 patients with prostatic carcinoma, obesity was an independent predictor of a high Gleason grade [10]. Obese patients with localized PC who underwent radical prostatectomy showed poorer outcome, shorter time to prostatic-specific antigen (PSA) failure, and higher recurrence rates afterwards than nonobese individuals [1,10]. Visceral adiposity measured by CT was associated significantly with a higher risk of PC as with each 1 SD increase in visceral fat, the risk of PC

increases more than 4.5 times [11,12]. Visceral fat acts as an endocrine organ secreting several inflammatory and carcinogenic proteins termed adipokines. These adipocytokines include adiponectin, leptin, resistin, vascular, endothelial growth factor, interleukin 6, and visfatin [13,14]. There is a growing body of evidence suggesting a strong association between adipokines and several malignancies such as colorectal, breast, endometrial carcinoma, and PC [7,15–18]. Researchers have reported that PC cell proliferation, invasion, and migration were boosted when exposed to sera from obese mice [7].

Visfatin, also called nicotinamide phosphoribosyltransferase (Nampt), is an enzyme that catalyzes the first step in the biosynthesis of nicotinamide adenine dinucleotide from nicotinamide. Visfatin, which is a protein, has also been reported to be a cytokine with a pre-B-cell colony-enhancing function (PBEF) that promotes B-cell maturation and inhibits neutrophil apoptosis [19,20]. Therefore, visfatin/PBEF/Nampt appears to be a multifunctional protein acting as a hormone, a cytokine, and/or an enzyme [21].

This enzyme occurs in two different forms: intracellular and extracellular (referred to as iNampt and eNampt, respectively). The function and secretion of eNampt have not been entirely understood. Visfatin (eNampt) is secreted by a nonclassical pathway in several different cell types, including differentiated adipocytes, macrophages, cardiomyocytes, and hepatocytes [22–24].

The association between obesity and PC remains poorly understood, but evidence suggests that obesity may adversely affect the risk of developing high-grade disease. Adipokines may contribute toward the molecular basis for a link between obesity and cancer prostate.

Several studies have shown the role of visfatin in different cancers including astrocytomas, myeloma, and male oral squamous cell; gastric, endometrial, hepatocellular, and colorectal carcinomas; and invasive breast cancer [25–28]. Recently, the role of Nampt/PBEF/visfatin in carcinogenesis and as a chemotherapeutic target has received attention.

In the present study, we attempted to investigate whether a high serum level of visfatin is a good biomarker associated with PC, especially high-grade cancer, and in obese patients; then, it could be used as a biomarker for detection of PC and to assess its aggressiveness.

Participants and methods

The present study included 89 individuals divided into the following groups: 15 age-matched volunteers, control group (group I), 36 patients diagnosed with benign prostatic hyperplasia (BPH group) (group II), and 38 patients diagnosed with PC (PC group) (group III). Informed consent was obtained from all the participants recruited before their inclusion in the study, which was approved by the clinical research ethics committee of faculty of medicine, Alexandria University, Egypt.

PC tissue specimens from all PC patients were examined and subjected to The Gleason Grading system to enable evaluation of the prognosis of men with PC; cancers with a higher Gleason score are more aggressive and have a worse prognosis.

BMI was calculated by dividing the participant's weight (kg) by his/her height (m^2). Venous blood samples were obtained from each participant after a 12-h overnight fasting. From each participant, 5 ml of whole blood was withdrawn into a plain vacutainer tube for separation of serum samples, which were kept frozen at −20 C until their use for measurement of visfatin, total PSA, and other routine lab investigations.

PSA was measured using a two-site, solid-phase chemiluminescent enzyme immunometric assay by the Immulite 1000 Automated Analyzer (Diagnostic Products Corporation, Siemens, USA) [29].

Routine laboratory investigations including assessment of fasting serum glucose, serum alkaline phosphatase activity, total cholesterol, triglycerides, aspartate aminotransferase activity, and creatinine were performed using the Olympus AU400 auto-analyzer: USA, RayBio Human Visfatin Enzyme Immunoassay with reconstituted freeze-dried forms of multianalyte calibrators for serum samples [30].

Serum visfatin concentration was determined using a commercial enzyme-linked immunosorbant assay RayBio Human Visfatin Enzyme Immunoassay (USA) [31] using the microplate reader. The intra-assay and interassay coefficient of variation was less than 10% and less than15%, respectively. The test kit is effective in the range of 0.1–1000 ng/ml.

Statistical analysis

Data were fed to the computer and analyzed using the IBM SPSS software package version 20.0. Qualitative data were described number and percent. Quantitative data were described as mean and SD for normally distributed data whereas abnormally distributed data

were expressed using median, minimum, and maximum. For normally distributed data, comparison between two independent populations was carried out using an independent *t*-test. For abnormally distributed data, comparisons between two independent populations were carried out using the Mann–Whitney *U*-test. Correlations between two quantitative variables were assessed using the Spearman coefficient. Multivariate linear regression was performed. Significance of the results obtained was assessed at the 5% level. To compare visfatin levels between tumor stages, the Kruskal–Wallis test was used. The correlation of serum visfatin with anthropometric parameters was analyzed using the Spearman rank order test. Differences with a *P* value less than 0.05 were considered significant.

Results

The clinical characteristics, some metabolic parameters as well as the serum visfatin concentration were compared between the three groups studied as shown in Table 1. PSA and BMI were significantly higher in the PC group compared with both the control group (P_3 < 0.001 and 0.013, respectively) and the BPH group (P_2 < 0.001 and 0.001, respectively).

There was a statistically significant increase in the serum visfatin concentration in PC patients (group III) compared with both the control group (group I) and patients with BPH (group II) (*P* < 0.001, *P* < 0.001, respectively) (Table 1). In PC patients, the median value of serum visfatin was 55.36 ng/ml (44.32–94.02) whereas it was 12.06 ng/ml (10.36–17.74) in the BPH group and 14.89 ng/ml (10.68–18.62) in the control group.

The PC group was studied in terms of the tumor stage using the Gleason score [32] and classified into three grades: low, intermediate, and high grade (Table 2). The mean value of the Gleason score among the PC cases was 6.58 ± 1.78.

There was no significant difference in the serum visfatin among the three grades (*P* = 0.12) (Table 3).

In Table 4, the PC group was classified according to their BMI into nonobese (<30 kg/m^2) and obese patients (>30 kg/m^2) and serum visaftin showed a significant increase in obese versus nonobese PC patients (76.50 ± 18.54 and 55.33 ± 8.09 ng/ml, respectively, *P* = 0.003). Moreover, when obese patients were compared with nonobese patients in the PC group, the Gleason score was found to be significantly higher in the obese versus the nonobese patients with PC (mean value of 8.80 ± 0.42 and 5.79 ± 1.34, respectively, *P* < 0.001)

Table 5 shows some statistical correlations that were performed to investigate the relationship between serum visfatin and PC as well as in PC patients, statistically positive correlations were found between visfatin and age (*r* = 0.425, *P* = 0.008) and BMI (*r* = 0.523, *P* = 0.001), but no signifi cant correlation was found between Visfatin and PSA (Table 5). Also, a significant positive correlation was found between visfatin and Gleason score (*r* = 0.378, *P* = 0.019) in the PC group (Table 5, Fig. 1), whereas no significant correlations were found between visfatin and other parameters in BPH patients (group II).

Linear regression analysis for factors affecting grade of PC showed that BMI, visfatin, and PSA were the major significant determinants of the tumor grade (Gleason score) [with a 95% confidence interval (CI) 0.096–0.233, *P* < 0.001; 0.083–0.016, *P* = 0.005; 0.001–0.019, *P* = 0.033, respectively].

A receiver operator characteristic (ROC) curve of serum visfatin against PSA (the well-established diagnostic marker of PC) was constructed. The area under the curve of visfatin was 1.00, whereas the area under the curve of PSA was 0.967 (Fig. 2). From the coordinates of the ROC curve, the diagnostic performances of serum visfatin and PSA were assessed

Table 1 Comparison between the three groups studied according to some clinical and laboratory parameters

Parameter	Control (*n* = 15)	BPH group (*n* = 36)	PC group (*n* = 38)	*P*
Age (years)	60.0 (55.0–69.0)	55.50 (37.0–88.0)	65 (48.0–84.0)[a,b]	0.217
PSA (ng/ml)	0.70 (0.40–0.90)	1.05 (0.21–17.0)[a]	45.90 (12.0–171.0)[a,b]	<0.001*
	P_1 = 0.003*, P_2 < 0.001*, P_3 < 0.001*			
Visfatin (ng/ml)	14.89 (10.68–18.62)	12.06 (10.36–17.74)[a]	55.36 (44.32–94.02)[a,b]	<0.001*
	P_1 < 0.001*, P_2 < 0.001*, P_3 < 0.001*			
BMI (kg/m^2)	22.79 ± 1.55	25.94 ± 3.46	29.15 ± 7.53[a,b]	0.001*
	P_1 = 0.063, P_2 < 0.001*, P_3 = 0.013*			

Normally distributed data were expressed as mean ± SD and were compared using the *F*-test (ANOVA), using post-hoc test (LSD); abnormally distributed data were expressed as median (minimum–maximum) and were compared using the Kruskal–Wallis test, using the Mann–Whitney *U*-test. BPH, benign prostatic hyperplasia; PC, prostate cancer; PSA, prostatic-specific antigen. P_1: *P* value for comparison between the control and the BPH group. P_2: *P* value for comparison between the BPH and the PC group. P_3: *P* value for comparison between the control and the PC group. *Statistically significant at $P \leq 0.05$.

and Youden's indices were calculated to obtain the best cut-off values.

The best cut-off value of serum visfatin was 17 ng/ml, with 100% specificity and 100% sensitivity, whereas the best cut-off value of PSA was 17.74 ng/ml, with 100% specificity and 94.74% sensitivity (Table 6).

Discussion

It is suggested that obesity is a significant risk factor for PC; in particular, aggressive disease and adipokines have been investigated as a link for this hypothesis [16]. On the basis of these studies as well as the previous findings of adipokine visfatin as a novel biomarker in various cancers such as glioblastoma, colon cancer, and gastric carcinoma [26,27], the present study attempted to assess the role of adipokine visfatin as a possible molecular mediator between obesity and PC progression.

In the present study, BMI was significantly higher in the PC group compared with both the control group (P_3 = 0.013, respectively) and the BPH group (P_2 < 0.001, respectively).

This was in agreement with several studies that identified obesity as a risk factor for PC [12,33,34], although the mechanisms underlying the association between obesity and PC are unclear.

Obesity and aggressiveness of prostate cancer

Progression of established PC has been associated with obesity and its metabolic sequelae. Evidence also suggests that obesity increases the aggressiveness of the disease [9]. Obesity is gaining recognition as an important risk factor for high-grade PC and also an increased risk of PC mortality compared with the nonobese population [35].

In our study, this finding was confirmed as obese PC patients showed more aggressive disease in the form of a higher Gleason score compared with nonobese PC patients (Table 4). Moreover, linear regression analysis showed that BMI was the major determinant of the tumor grade of PC (95% CI, 0.096–0.233, P < 0.001) (Table 6). Also, a significant positive correlation was found between BMI and grade of PC (Gleason score) in the PC group (r = 0.728, P < 0.001) (Table 6).

In a study carried out by researchers from Prince Margret Hospital, it was found that an increase in BMI was associated independently with an increased risk of both pathologic progression (95% CI, 1.1–2.1; P = 0.02) and therapeutic progression (95% CI, 1.0–1.9; P = 0.05) of surveyed patients with low-grade PC [36].

There is growing evidence to suggest that adipokines may play an important role in mediating this association between obesity and high-grade PC [16].

Furthermore, adipokines have been associated with PC and the body of evidence is growing particularly in relation to visfatin and PC [37].

Table 2 Distribution of the prostate cancer cases studied according to the Gleason score

Gleason score	*N* (%)
Low grade (4–6)	20 (52.6)
Intermediate grade (7)	4 (10.5)
High grade (8–10)	14 (36.8)
Minimum–maximum	5.0–9.0
Mean ± SD	6.58 ± 1.78
Median	5.0

Serum visfatin and prostate cancer

In the present study, we have investigated the possible role of the adipokine visfatin in PC. We found a statistically significant increase in serum visfatin concentration in PC patients (group III) compared with both the control group (group I) and patients with BPH (group II) (P < 0.001, P < 0.001, respectively) (Table 1). To the best of our knowledge, there has been no report comparing the serum level of visfatin between PC and BPH. This analysis may provide additional information on the role of visfatin in PC, its tumor grade, and the possible use of visfatin as a therapeutic target.

To compare the diagnostic performance of serum visfatin with PSA (the well-established diagnostic marker of PC) in differentiating between PC and BPH, ROC curves were constructed and the best generated cut-off values were calculated (17 and 17.74 ng/ml, respectively). The area under the curve

Table 3 Relation between the Gleason Score and visfatin in the prostate cancer group

Visfatin (ng/ml)	Gleason score			
	Low	Intermediate	High grade	*P*
Minimum–maximum	44.32–76.44	56.95–63.57	51.22–94.02	0.120
Mean ± SD	54.84 ± 9.13	60.26 ± 3.82	69.74 ± 19.02	
Median	52.05	60.26	55.36	

P value for the Kruskal–Wallis test

Table 4 Relation between BMI with visfatin and the Gleason score in the prostate cancer group

Parameter	BMI		*P*
	<30 (*n* = 28)	≥30 (*n* = 10)	
Visfatin (ng/ml)			
Minimum–maximum	44.32–76.44	54.77–94.02	$^{MW}P = 0.003^{*}$
Mean ± SD	55.33 ± 8.09	76.50 ± 18.54	
Median	54.61	88.88	
Gleason score [*n* (%)]			
Low grade	20 (71.4)	0 (0)	$^{MC}P < 0.001^{*}$
Intermediate grade	4 (14.3)	0 (0)	
High grade	4 (14.3)	10 (100)	
Minimum–maximum	5.0–9.0	8.0–9.0	$^{MW}P < 0.001^{*}$
Mean ± SD	5.79 ± 1.34	8.80 ± 0.42	
Median	5.0	9.0	

^{MW}P: *P* value for the Mann–Whitney *U*-test. ^{MC}P: *P* value for the Monte Carlo test. *Statistically significant at $P \leq 0.05$.

of visfatin (1.00) was larger than that of PSA (0.967) (Fig. 2). This indicated that serum visfatin surpassed PSA in diagnosing PC. This was also proved by the presence of a higher degree of diagnostic sensitivity (100 vs. 94.74%, respectively) and negative predictive value (100 vs. 94.74%, respectively) (Table 6). Thus, in our study, visfatin proved to be more valuable as a sensitive marker for the detection of PC than PSA.

At the cellular level, the relationship between visfatin and PC has been established. Wang *et al.* [37] found that increased visfatin (iNampt) expression in early PC and its inhibition suppressed cell growth in culture, cell invasion, and the growth of xenografted PC cells in mice. Several researchers found that visfatin

Table 5 Correlation between visfatin with different parameters in each group

Parameter	BPH group (*n* = 36)		PC group (*n* = 38)		Total patients (*n* = 74)	
	r_s	*P*	r_s	*P*	r_s	*P*
Age	0.059	0.732	0.425*	0.008	0.410*	<0.001
PSA	0.322	0.055	0.237	0.153	0.816*	<0.001
Gleason score	—	—	0.378*	0.019	0.378*	0.019
BMI	–0.237	0.163	0.523*	0.001	0.147	0.210
FBS	0.150	0.382	0.309	0.059	0.337*	0.003

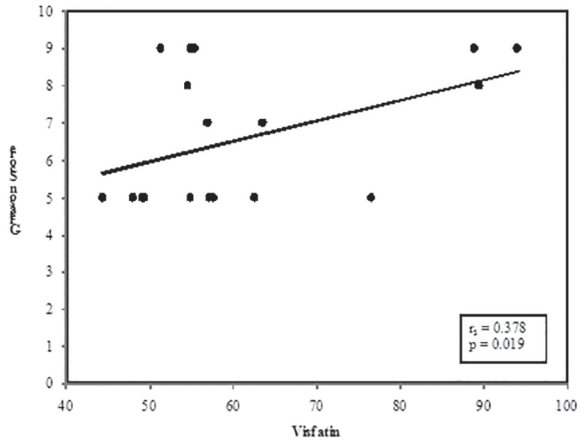
BPH, benign prostatic hyperplasia; PC, prostate cancer; PSA, prostatic-specific antigen; r_s, Spearman coefficient. *Statistically significant at $P \leq 0.05$.

Table 6 Agreement (sensitivity, specificity, and accuracy) for prostatic-specific antigen and visfatin with the prostate cancer group (*n* = 74)

Parameter	BPH	PC	Sensitivity	Specificity	PPV	NPV	Accuracy
PSA (ng/ml)							
≤17	36	2	94.74	100.0	100.0	94.74	97.30
>17	0	36					
Visfatin (ng/ml)							
≤17.74	36	0	100.0	100.0	100.0	100.0	100.0
<17.74	0	38					

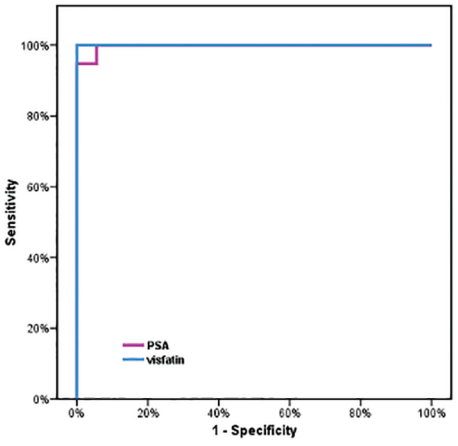
BPH, benign prostatic hyperplasia; PC, prostate cancer; PSA, prostatic-specific antigen.

Figure 1



Correlation between visfatin and the Gleason score in the prostate cancer group.

Figure 2



Receiver operator characteristic curve for prostatic-specific antigen and visfatin for the diagnosis of prostate cancer patients.

expression confers resistance to chemotherapeutic agents, including fluorouracil, doxorubicin, paclitaxel, etoposide, and phenylethyl isothiocyanate [26,37,38].

Thus, it has been shown that visfatin plays a role in PC and the effect appeared to be mediated by exogenously applied visfatin. It was therefore logical to evaluate the levels of circulating plasma visfatin in patients with PC and its relation to the tumor grade to evaluate its potential use as a potential biomarker.

In the present study, the relationship between serum visfatin and aggressiveness of PC was assessed by a comparison among the three grades of Gleason score in PC patients. Although there was no statistically significant difference in the serum visfatin among the three grades (P = 0.12) because of the low number of PC patients in the study, the mean value of serum visfatin showed a gradual increase with increasing tumor grade (54.84 ± 9.13, 60.26 ± 3.82, and 69.74 ± 19.02 ng/ml) in low, intermediate, and high grades, respectively (Table 3). There have been no reports on the serum level of visfatin in PC patients and no data on its role in the progression of PC found, and this was the subject that this study attempted to focus on.

Visfatin has been shown to modulate proliferation, apoptosis, and angiogenesis [17]. At the cellular level, both normal prostate cells and androgen-sensitive PC cell lines expressed visfatin mRNA with a predominantly cytoplasmic distribution [16–19].

In our study, we also found a significant positive correlation between serum visfatin and the Gleason score in the PC group (r = 0.378, P = 0.019) (Table 5, Fig. 1).

In a previous study, it was found that expressions of matrixmetalloproteinase-2 and 9 were induced by visfatin within the androgen-sensitive PC cell lines [17]. Cellular proliferative correlated with lymph node metastases and the absence of estrogen and progesterone receptors [39]. The effect of visfatin was shown to be concentration dependent, suggesting a role for its circulating plasma level.

The study of visfatin in other cancers showed its association with the aggressiveness and progression of some malignancies. Higher eNampt levels correlate with myometrial invasion and shorter patient survival in women with endometrial carcinoma [27]. Also, higher eNampt levels were observed in invasive breast cancer.

Furthermore, levels of visfatin have been documented to be increased in obesity as have other adipokines. In our study, serum visaftin showed a significant increase in obese versus nonobese PC patients (76.50 ± 18.54 and 55.33 ± 8.09 ng/ml, respectively, P = 0.003).

In PC patients, a statistical positive correlation was found between visfatin and BMI (r = 0.523, P = 0.001) (Table 4)

This may be one mechanism by which obesity is linked to PC, but we cannot document that it is the only mechanism.

Conclusion

According to the findings of the present study mentioned above, we found a statistically significant increase in the serum visfatin concentration in PC patients compared with both the controls and patients with BPH. Also, serum visfatin showed a significant increase in obese versus nonobese PC patients. A significant positive correlation was found between visfatin and the Gleason score. The mean value of serum visfatin showed a gradual increase with increasing tumor grade.

In this study, we found a significant positive association between serum visfatin and PC especially in obese participants, and it may be also a risk factor for high-grade PC. Therefore, visfatin could be used as a new promising biomarker for both the diagnosis of PC and for the assessment of its aggressiveness.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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