

Altered circulating levels of adipokine omentin-1 in patients with prostate cancer

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Background: Prostate cancer (PCa), one of the most common cancers in men, accounts for nearly 20% of adult malignant neoplasms. Omentin-1 is synthesized in visceral adipose tissue and its concentration in plasma changes with cancers. However, the association between omentin-1 and PCa was rarely studied. Thus, we investigated the plasma omentin-1 levels in PCa patients in Chinese population.

Materials and methods: Ninety cases of PCa and 90 matched healthy controls were enrolled in this study. We used ELISA technique to determine the concentration of omentin-1.

Results: The concentration of omentin-1 was higher in patients with PCa compared to controls ($P < 0.001$). Additionally, positive correlations were uncovered between omentin-1 with body mass index ($r = 0.240$, $P = 0.001$), waist-hip ratio ($r = 0.228$, $P = 0.002$), and prostate-specific antigen ($r = 0.589$, $P < 0.001$). Receiver operating characteristic curve analysis indicated that plasma omentin-1 differentiated PCa patients from controls with a sensitivity of 85.9% and a specificity of 83.7%.

Conclusion: Our study demonstrated that the levels of plasma omentin-1 were increased in PCa patients. Meanwhile, omentin-1 may be a possible biomarker for diagnosing PCa. For validation, more studies should focus on and elucidate the potential mechanism underlying this change.

Keywords: omentin-1, prostate cancer, obesity, body mass index, adipokines

Background

Prostate cancer (PCa) is one of the most common urological neoplasms, which accounts for nearly 20% of malignant tumors in male in America.¹ Although People's Republic of China reported a lower incidence rate of PCa, the past decades had witnessed the increasing morbidity of PCa in Chinese population.² Thus, there is a pressing need that more studies should focus on PCa including early diagnosis. Gradually, accumulative proofs have verified that genetic alternations and other etiology risk factors, such as processed fat intake, red meat consumption, superfluous nutrients, and obesity are considered to add the risk of PCa in a complicated style.³

In the past few decades, it had been discovered that the potential role of obesity promoted the process of carcinogenesis. And roughly 20% of all cancers were related to excess weight gain, and this data may be underestimated.^{4,5} For example, the relationships between breast cancer, pancreatic cancer, rectal cancer, and obesity had been found.^{6,7} Although studies reported controversial correlations between obesity and PCa, obesity was still considered as a relevant risk factor in giving rise to the higher morbidity of PCa,⁸ which was also confirmed by several large

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meta-analyses.^{9,10} Many factors, such as insulin, insulin-like growth factor-I, and adipokines might take critical parts in the relationship between obesity and cancers.^{11,12} Among the many factors, the effects of adipokines in promoting tumorigenesis and progression have been put forward recently. Adipokines, including visfatin, adiponectin, leptin, and resistin are bioactive molecules secreted by adipose cells and have been implied to be involved in obesity's association with PCa.^{13,14}

Recently, one of the adipokines, omentin-1, was investigated extensively. Omentin-1 was originally discovered named "intelectin", which was separated from intestine paneth cells at first.¹⁵ Omentin-1 is a 34 kDa protein. It was a kind of depot-specific adipokine with higher expression and release from visceral depots compared with subcutaneous adipose tissue.¹⁶ Several related researches reported that altered circulating concentrations of omentin-1 in colorectal cancer and renal cell cancer patients, which indicated that omentin-1 might play a potential role in carcinogenesis.^{17,18} However, to our knowledge, plasma omentin-1 levels in PCa were rarely explored, especially in Asian population.^{19,20} Herein, we conducted this case-control study to test the plasma omentin-1 levels in PCa in Chinese population and to explore its potential role in diagnosing PCa patients.

Materials and methods

Patients

The present study was conducted in accordance with the Declaration of Helsinki and authorized by the Ethics Committee of the First Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong, People's Republic of China. All candidates provided informed consent to allow analysis of data for research purposes. In the calculation, the minimum total sample size was measured as 52 and a minimum of 26 for PCa and control group, respectively. In total, between July 2016 with July 2017, 90 patients newly diagnosed with PCa who underwent 12-core trans-rectal ultrasound (TRUS) guided prostate biopsy at the First Affiliated Hospital of Guangdong Medical University were recruited in our study. All patients were assessed for elevated prostate-specific antigen (PSA) (>4 ng/mL) or abnormal digital rectal examination for TRUS prostate biopsy. In all patients, prostate was routinely biopsied near base, mid-gland, and apex, bilaterally, with six biopsies per side. Patients with PCa were arranged to three

groups by Gleason score: well differentiation (Gleason score <7), moderately differentiation (Gleason score $=7$), and poorly differentiation (Gleason score >7). Meanwhile, 90 age-matched volunteers were selected as healthy controls from people who visited the Affiliated Hospital of Guangdong Medical University for a routine check-up. All patients were recruited using regular criteria: no curative medication for PCa; no history of malignancy or prostate operations; no diagnosis of acute infectious diseases; and no impairment of heart, liver or kidney. Peripheral venous blood samples were collected from all patients and controls after fasting for at least 12 hrs. Whole blood was centrifuged with 8000 rpm at 4°C for 30 mins and the supernatants were collected. All the samples were put into 1.5 mL eppendorf tubes and preserved at -80°C until testing.

Physical and biochemical measurements

Anthropometric measurements were collected in the present study, including height, weight, waist and hip circumference. The body mass index (BMI) was calculated as the weight divided by the square of the height (kg/m^2). Waist-hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Biochemical parameters were detected in previously stored plasma samples. The plasma levels of total cholesterol (TC), triacylglycerol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) concentrations, fasting blood glucose (FBG), creatinine, blood urea nitrogen (BUN) and PSA were measured using the standard methods by a chemistry analyzer (Shimadzu, CL8000, Japan).

Plasma omentin-1 concentration determination

Levels of omentin-1 detected in plasma samples reserved through an ELISA assay according to the user manual (omentin-1: CUSABIO, CSB-E09745h, People's Republic of China). The detection range of the assay was 1.56–100 pg/mL (omentin-1). The precision of this assay: intra-assay precision $<8\%$ and inter-assay precision $<10\%$.

Statistical analysis

The software used in the study was IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA) for statistical analyses. Quantitative characteristics were described as mean \pm SE. One-way analysis of variance and the nonparametric Kruskal–Wallis test were used for comparisons of groups

and subgroups. Subsequently, Pearson's (normally distributed) or Spearman's correlation analyses were performed to test the correlations between omentin-1 levels and previously mentioned clinical and biochemical parameters. The accuracy of omentin-1 to differentiate PCa from control was assessed by receiver operating characteristic (ROC) curve analysis. For all analyses, a two-tailed $P < 0.05$ was considered significant.

Results

Studied groups

The general characteristics information including anthropometric measurements and biochemical parameters of PCa individuals (90 subjects) and the healthy individuals (90 subjects) were included in Table 1. No statistically significant difference was found in age ($P=0.469$), BMI ($P=0.083$), WHR ($P=0.057$), FBG ($P=0.064$), HDLC ($P=0.896$), LDLC ($P=0.169$), creatinine ($P=0.468$), and BUN ($P=0.264$) between the groups. TC (4.68 ± 0.81 vs 4.41 ± 0.94 ; $P=0.035$), triacylglycerol (1.32 ± 0.60 vs 1.51 ± 0.55 ; $P=0.034$), and PSA (1.13 ± 0.44 vs 36.80 ± 35.44 ; $P < 0.001$) levels were significantly lower in the healthy controls group than the PCa patients.

Plasma levels of omentin-1

Plasma concentrations of omentin-1 in PCa group and healthy controls were all detectable. Plasma omentin-1 concentrations were detected to range from 0.014 to 21.854 ng/mL with a mean of 4.96 ng/mL for healthy controls and range from 0.377 to 40.393 ng/mL with a mean of 12.94 ng/mL for PCa

patients (Table 1). As shown in Figure 1, PCa patients had significantly higher plasma omentin-1 levels compared to the healthy individuals ($P < 0.001$). To exclude the probable impact of BMI on omentin-1 levels, we tested the statistical difference of BMI between three groups divided by tumor grade. As a result, no statistical differences were observed between the groups about the BMI ($F=0.039$, $P=0.962$). In addition, we did not find a significant relationship between the tumor grades of PCa and the omentin-1 level ($P=0.873$) (Table 2).

Spearman correlation analysis

As a result, there was a positive correlation between omentin-1 level and BMI value in PCa group ($r=0.291$, $P=0.005$) and whole group ($r=0.240$, $P=0.001$), respectively. Another obesity-related parameter WHR was also found to be positively correlated with omentin-1 level in healthy controls ($r=0.216$, $P=0.038$), PCa patients ($r=0.219$, $P=0.036$), and whole ($r=0.228$, $P=0.002$). Besides, positive correlation was also observed between omentin-1 level and PSA ($r=0.589$, $P < 0.001$) (Table 3). Our result demonstrated that plasma levels of omentin-1 were not significantly correlated with other parameters, including age, FBG, HDLC, LDLC, TC, Triacylglycerol, creatinine, and BUN levels in the whole group.

ROC curve analysis

ROC curve was applied to assess the performance of plasma omentin-1 level in distinguishing PCa individuals from healthy controls. In Figure 2, we showed the ROC curve of the investigated plasma omentin-1. The area under the ROC curve is 0.872. With a cutoff point of 8.196 ng/mL for plasma

Table 1 Comparison of general characteristics and biochemical parameters

Variables	HC group (n=90)	PCa group (n=90)	T or Z ^Δ value	P-value
Age (years)	71.34±6.29	72.07±7.29	-0.726	0.469
BMI (kg/m ²)	24.76±3.00	25.64±2.73	-1.745	0.083
WHR	0.90±0.26	0.91±0.38	-1.917	0.057
PSA (ng/mL)	1.13±0.44	36.80±35.44	-9.651 ^Δ	<0.001*
FBG (mmol/L)	5.41±0.78	5.66±1.02	-1.862 ^Δ	0.064
HDLC (mmol/L)	1.38±0.36	1.39±0.37	-0.131	0.896
LDLC (mmol/L)	2.70±0.82	2.86±0.80	-1.381	0.169
TC (mmol/L)	4.68±0.81	4.41±0.94	2.119	0.035*
Triacylglycerol (mmol/L)	1.32±0.60	1.51±0.55	-2.131	0.034*
Creatinine (μmol/L)	75.18±14.84	73.66±13.48	0.728	0.468
BUN (mmol/L)	5.81±1.34	6.04±1.40	-1.119	0.264
Omentin-1 (ng/mL)	4.96±4.71	12.94±6.15	-9.871	<0.001*

Notes: * $P < 0.05$. Data are presented mean±SE.

Abbreviations: HC, healthy control; PCa, prostate cancer; BMI, body mass index; WHR, waist-hip ratio; PSA, prostate-specific antigen; FBG, fasting blood glucose; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; BUN, blood urea nitrogen.

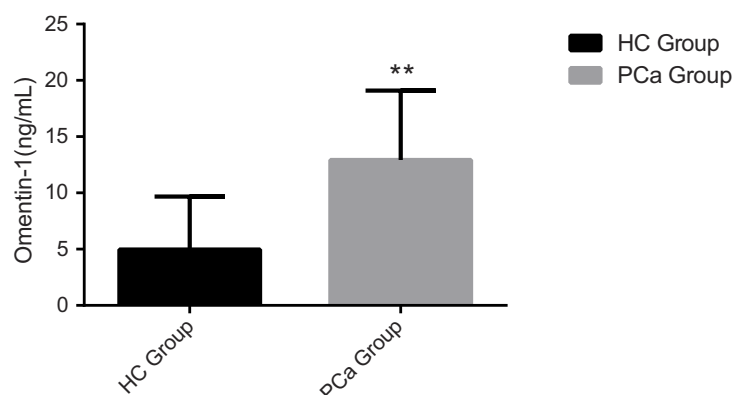


Figure 1 The omentin-1 levels in the healthy control (HC) subjects (n=90) and prostate cancer (PCa) patients (n=90). ** $P < 0.001$.

Table 2 One way ANOVA analysis on omentin-1 levels with PCa status

PCa status	Mean \pm SE (ng/mL)	N	F value	P-value
Well-differentiated (Gleason score<7)	12.51 \pm 2.65	27	0.136	0.873
Moderately differentiated (Gleason score=7)	12.22 \pm 2.52	29		
Poorly differentiated (Gleason score>7)	12.22 \pm 2.29	36		

Abbreviation: PCa, prostate cancer.

Table 3 Pearson's or Spearman's correlation coefficient analysis of omentin-1 levels with general clinical characteristics and biochemical parameters

Variables	HC group		PCa group		Whole group	
	Correlation coefficient (r)	P-value	Correlation coefficient (r)	P-value	Correlation coefficient (r)	P-value
Age (years)	-0.080	0.450	-0.041	0.696	-0.014	0.852
BMI (kg/m ²)	0.114	0.281	0.291	0.005*	0.240	0.001*
WHR	0.216	0.038*	0.219	0.036*	0.228	0.002*
PSA (ng/mL)	0.116	0.271	0.001	0.994	0.589	<0.001*
FBG (mmol/L)	0.007	0.945	-0.054	0.610	0.061	0.411
HDLc (mmol/L)	-0.266	0.010*	0.043	0.687	-0.066	0.375
LDLC (mmol/L)	0.034	0.750	0.098	0.354	0.115	0.119
TC (mmol/L)	0.011	0.914	-0.018	0.867	-0.096	0.193
Triacylglycerol (mmol/L)	-0.022	0.832	-0.089	0.400	0.046	0.535
Creatinine (μ mol/L)	-0.083	0.430	0.004	0.967	-0.055	0.457
BUN (mmol/L)	-0.048	0.650	0.170	0.106	0.111	0.134

Note: * $P < 0.05$

Abbreviations: HC, healthy control; PCa, prostate cancer; BMI, body mass index; WHR, waist-hip ratio; PSA, prostate-specific antigen; FBG, fasting blood glucose; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; BUN blood urea nitrogen.

omentin-1 concentrations, we were able to distinguish PCa patients from controls with a sensitivity of 85.9%, and a specificity of 83.7%.

Discussion

As is known to the public, PCa is becoming an increasingly noticeable public health problem. Described in the

very recent cancer statistics, PCa was thought to account for about 19% of all cases of cancers newly diagnosed and 9% of cancer-related deaths in men in America.¹ And there was a gradual rise in the incidence rates of PCa and obesity in many countries, with a diet habits rich of high fat, sugar, and cholesterol.²¹ Therefore, the similar morbidity trends of PCa and obesity suggested the probable

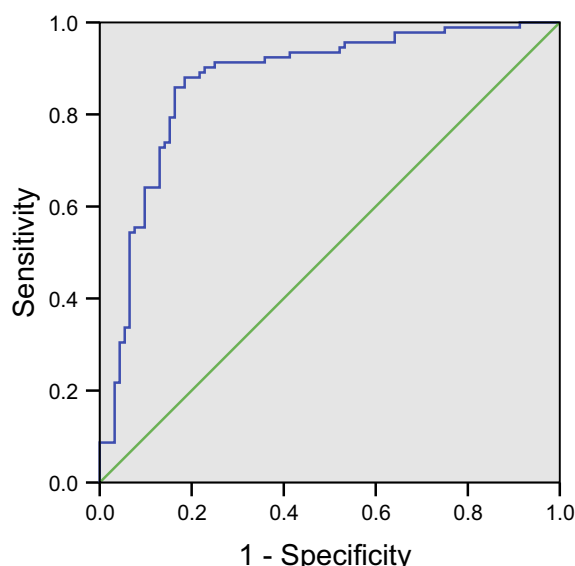


Figure 2 ROC curve analysis assessed the performance of omentin-1 levels in diagnosing prostate cancer. The area under the ROC curve (AUC) for omentin-1 was 0.883, $P < 0.001$.

relevance between them. Yet, the correlation between obesity and PCa occurrence was complicated and indicated conflicting conclusions. Park et al reported that obesity may be an independent risk factor of higher incidence of PCa,²² which was supported by another two studies.^{23,24} Moreover, previous meta-analysis demonstrated the correlation between high BMI and high incidence of PCa.^{9,10} Interestingly, there were also some other studies arguing that BMI was not a risk factor of PCa.^{25,26}

Many hypotheses are trying to address the questions about the correlation between cancer incidence and obesity. Among these factors, the involvement of adipokines, including resistin, apelin, and leptin played an important role in the process of microenvironment chronic inflammation. The chronic inflammation in the microenvironment could promote the tumor initiation and progression.^{27,28} For instance, leptin exhibited a role of promoting the incidence of PCa. The potential mechanism may be the function of leptin to induce the lesions of prostatic intraepithelial and the inhibition of apoptosis.²⁹

In recent years, omentin-1 was known to be one of the adipokines enriched in human adipose tissue. Several studies demonstrated that patients diagnosed with polycystic ovary syndrome who indicated higher BMI showed lower concentration of omentin-1 compared to the healthy group.^{30,31} Moreover, other researches about colorectal cancer and renal cell carcinoma elaborated the regulatory effects of obesity.^{17,18}

Concretely, Fazeli et al observed a higher concentration of omentin-1 in colorectal cancer patients compared with controls.¹⁷ However, Shen et al reported lower plasma concentrations of omentin-1 in renal cell carcinoma patients than healthy controls.¹⁸ Furthermore, Uyeturk et al conducted the only research about the omentin-1 in PCa in Turkey population and reported a higher plasma omentin-1 concentrations in PCa patients than benign prostatic hyperplasia (BPH) patients.¹⁹ Also, Fryczkowski et al tested the omentin level in Poland population, and found higher plasma omentin levels in PCa patients than BPH patients.²⁰ In the present study, we observed that PCa patients had significantly higher circulating omentin-1 levels of 12.94 ± 6.15 ng/mL than the healthy control group of 4.96 ± 4.71 ng/mL ($P < 0.001$). Then, Pearson or Spearman correlation analysis revealed that circulating omentin-1 concentrations positively correlated with PSA, BMI, and WHR. Previous studies were conflicted regarding the role of omentin-1 in cancers and its association with obesity. Fazeli et al suggested a significant correlation between circulating omentin-1 concentrations and colorectal cancer, which was independent of obesity.¹⁷ Shen et al argued plasma omentin-1 concentrations were obviously decreased in renal cell carcinoma patients, and negatively correlated with BMI.¹⁸ Our result found that omentin-1 concentrations were positively correlated with BMI and WHR, which were intrinsic indicators of obesity, in PCa patients.¹⁹

In our study, patients with high-grade tumors were not found to have significant elevation of omentin-1 levels. Similarly, Uyeturk et al also reported no significant association between the differentiation grades of PCa and the omentin level,¹⁹ suggesting omentin-1 may not be a marker of aggressiveness. Consistent with our study, Shen et al also indicated that plasma omentin-1 concentrations were not correlated with the TNM staging ($T_{1-4}N_0M_0$) of renal cancer.¹⁸ Besides, Fazeli et al also demonstrated that colorectal cancer patients' circulating omentin-1 concentrations were not related to the TNM staging.¹⁷ Thus, there was a similarity in studies regarding the function of omentin-1 in pathogenesis of cancer with different studies on plasma omentin-1 with respect to grades of the disease.

Up till now, the definite pathogenesis of omentin-1 in tumorigenesis has not been illuminated clearly. Zhang et al revealed a possible mechanism about cancer and omentin-1. In their study, hepatocellular carcinoma proliferation was suppressed. They also found p21 protein upregulated

in hepatocellular carcinoma cells. And in return, the expression of a tumor suppresser gene-related protein p53 increased.³² In addition, omentin-1 promoted hepatocellular carcinoma apoptosis by upregulating the bax-to-bacl-2 ratio and inhibiting capases-3 activation.³² Besides, recent studies demonstrated omentin-1's effect on enhancing Akt phosphorylation/activation.^{16,33} Meanwhile, the PI3K/Akt-eNos Ras pathway participated in the process of colorectal tumor incidence.³⁴ Obviously, what can be hypothesized is that omentin-1 may facilitate the activation of the Akt signaling pathway and subsequently modulate eNOS, thereby contribute to the process of pathogenesis of colorectal cancer.^{35–37} So, more studies will be needed to illuminate the definite roles of omentin-1 in PCa and other malignancies.

Conclusion

In summary, omentin-1 concentrations were observed to be significantly elevated in PCa patients. Circulating omentin-1 concentrations positively correlated with obesity-related markers BMI and WHR. These findings indicated that omentin-1 may have a potential role in the development of PCa through mechanisms that play an important part in the association of obesity and PCa. This study suggested that the plasma omentin-1 may assist in the diagnosis of PCa. For validation, more studies would be needed to shed light on the potential mechanisms about this increase and to evaluate the interplay between PCa and obesity, which may further provide promising and novel pharmacological insights for PCa diagnosis and therapy in the near future.

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Disclosure

The authors report no conflicts of interest in this work.

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