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Original Article

Circulating levels of adiponectin and leptin in patients with prostate cancer

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Abstract: Prostate cancer (PCa) is one of the major health care problems in males. It is known that red and processed meat consumption, fat intake and obesity are risk factors for PCa development. Adiponectin and leptin are adipokines that are synthesized in visceral adipose tissue and associated with obesity. Up to date, the association of serum adiponectin and leptin with PCa largely remains unexplored. Therefore, we studied the concentration of adiponectin and leptin in PCa patients in Chinese population. 92 prospective cases of prostate cancer and 92 matched healthy controls were enrolled in this study. Serum adiponectin and leptin levels were detected by enzyme-linked immunosorbent assays (ELISA) technique. No statistically significant differences were observed in age, body-mass index (BMI), prostate specific antigen (PSA), fasting blood glucose (FBG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), creatinine (CRE), and blood urea nitrogen (BUN) in the paired groups. Both serum adiponectin and leptin levels were significantly higher in patients with PCa compared to healthy controls (P<0.001 for both). Subsequently, there was a positive correlation between adiponectin and PSA (r=0.285, P<0.001). Positive significant correlations between BMI, PSA, TG and leptin were also observed in whole group (r=0.270, P<0.001; r=0.348, P<0.001; r=0.170, P=0.021, respectively). However, the serum adiponectin and leptin levels were not related to the Gleason score of PCa. Receiver operating characteristic curves analysis of the investigated serum adiponectin differentiated cancer patients from the healthy individuals with a sensitivity of 87%, specificity of 56%. Leptin levels also distinguished patients from the healthy controls with a sensitivity of 69%, specificity of 68%. Our study shows that the serum levels of adiponectin and leptin in PCa patients were higher than healthy controls. Adiponectin and leptin may be important markers of PCa. For validation, further studies including large cohort studies would be required.

Keywords: Prostate cancer, circulating biomarkers, adiponectin, leptin, ELISA

Introduction

Prostate cancer (PCa) is becoming an increasingly noticeable public health problem, especially for those countries with an aging society. As it was described in the very recent cancer statistics, PCa is estimated to account for about 21% of all cases of cancers newly diagnosed and 8% of cancer-related deaths in men in America [1]. Although China was reported to have a lower incidence rate of PCa, the incidence in China has already increased steadily over the past few decades [2]. The etiology of PCa is largely inconclusive. Accumulative proofs have verified that genetic alternations and other etiology risk factors such as red and processed meat consumption, fat intake, related nutrients, and obesity are considered to be risk factors to develop PCa in a complex manner [3]. Over the past few decades, the potential role of obesity in promoting the process of carcinogenesis has been gradually discovered. It has been estimated that roughly 20% of all cancers were caused by excess weight gain, and this percent may be underestimated [4, 5] and the relationship between rectal cancer, renal cancer and obesity has been revealed [6, 7]. Although individual studies were conflicted regarding the association between obesity and PCa, obesity is believed to be an increasingly prevalent factor in contributing to the high incidence of PCa, and some large meta-analyses

have reported that obesity was related to a modestly increasing incidence of PCa [8, 9]. However, the potential mechanisms between cancer development and obesity are largely undiscovered. Several studies have elucidated that a variety of physiological and pathological processes such as insulin resistance, hyperinsulinemia, sustained hyperglycemia, glucose intolerance, oxidative stress, inflammation and/or adipokine production were well-recognized risk factors contributing to the link of obesity to cancer association and determining the patients' risks [10]. Among the various factors, the participation of adipokines has been proposed recently. Adipokines are secreted by adipose tissue which is currently considered as a complex and crucial endocrine organ in cancer development. It has been indicated the aberrant adipokines production of adipose tissue may result in chronic inflammation in the microenvironment and thereby initiate or promote carcinogenesis [11]. Several adipokines such as omentin-1, adiponectin and leptin are biologically active polypeptides produced by adipocytes and have been shown to be involved in obesity's association with PCa [12, 13].

Adiponectin is secreted exclusively from adipose tissue, which is encoded by the gene AdipoQ and makes a protein 244 amino acids in length that is 30 kDa in weight [14]. It has been shown that adiponectin played vital roles in anti-atherosclerosis, anti-insulin resistance [14-16]. Leptin is a protein that is 16 kDa in weight and 167 amino acids in length [17]. Indeed, research suggests that leptin played a role in the progression of mammary tissue tumorigenesis via its function as a growth hormone [18]. Importantly, an inverse correlation between reduced adiponectin and obesity and a positive correlation between leptin levels and obesity had been reported [19, 20].

In addition, several studies have reported increased or decreased circulating adiponectin and leptin levels in colorectal, breast, pancreatic, ovarian, and lung cancer patients [15, 19, 21, 22], indicating a underlying role with tumorigenesis. Currently, to our knowledge, circulating levels of adiponectin and leptin in PCa patients are largely unexplored in Asian area, especially in Chinese population. Herein, we conduct this matched case-control study to determine the serum levels of adiponectin and leptin in patients with PCa in Chinese population.

Materials and methods

Patients and healthy controls

Between June 2014 and June 2015, 92 patients newly diagnosed with PCa and who underwent trans-rectal prostate biopsy at the first affiliated hospital of Anhui Medical University were enrolled in this study. Patients with PCa were divided into three groups according to grades (low, intermediate, and high grade determined by a Gleason score of less than 7, 7 and more than 7, respectively). Meanwhile, 92 age-matched volunteers were selected as healthy controls from people who confirmed their fitness at the health examination center of the first affiliated hospital of Anhui Medical University. This study was approved by the Ethics Committee of the first affiliated hospital of Anhui Medical University, Hefei, Anhui, People's Republic of China. All candidates provided written informed consent to allow analysis of data for research purposes.

All patients were recruited using the following criteria: no curative medication for prostate diseases; no history of malignancy or prostate operations; no diagnosis of acute infectious diseases, and no impairment of heart, liver or kidney. Venous blood samples were drawn from all patients and controls after fasting for at least 12 hours. Hemolytic, lipaemic or icteric samples were discarded. Samples were then centrifuged with 8000 rpm at 4°C for 4 minutes and the supernatant was collected. All the serum were kept in polypropylene tubes and stored at -80°C until detection.

Physical and biochemical measurements

Anthropometric measurements obtained in this study included height, weight. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Biochemical parameters were measured in the stored serum samples. The serum levels of total cholesterol (TC), triacylglycerol (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) levels, fasting blood glucose (FBG), creatinine (CRE), blood urea nitrogen (BUN) and prostate specific antigen (PSA) were detected using the standard

Table 1. Comparison of general characteristics and biochemical parameters

Variables	Prostate cancer group (n=92)	Healthy control group (n=92)	T or Z$^{\Delta}$	*P* value
Age (years)	72.20±6.15	70.88±5.45	1.535	0.126
BMI (kg/m^2)	24.08±3.01	24.42±2.87	-0.793	0.430
PSA (ng/mL)	36.80±35.44	1.13±0.44	-11.719$^{\Delta}$	**<0.001**
FBG (mmol/L)	5.92±1.18	6.04±1.67	-0.588	0.557
HDL-C (mmol/L)	1.48±0.36	1.37±0.32	2.187	**0.030**
LDL-C (mmol/L)	2.86±0.80	2.70±0.82	1.381	0.169
TC (mmol/L)	4.41±0.94	4.54±0.91	-1.002	0.318
TG (mmol/L)	1.51±0.55	1.36±0.58	1.749	0.082
CRE (μmol/L)	80.08±22.91	77.87±14.76	0.777	0.438
BUN (mmol/L)	6.04±1.40	5.81±1.34	1.119	0.264
Adiponectin (μg/mL)	20.32±12.09	14.56±11.72	-3.758$^{\Delta}$	**<0.001**
Leptin (ng/mL)	6.28±7.28	2.44±2.52	-5.177$^{\Delta}$	**<0.001**

Bold values are statistically significant P<0.05. Abbreviations: BMI body mass index, PSA prostate-specific antigen, FBG fasting blood glucose, HDL-C high density lipoprotein-cholesterol, LDL-C low density lipoprotein-cholesterol, TC total cholesterol, TG triacylglycerol, CRE creatinine, BUN blood urea nitrogen.

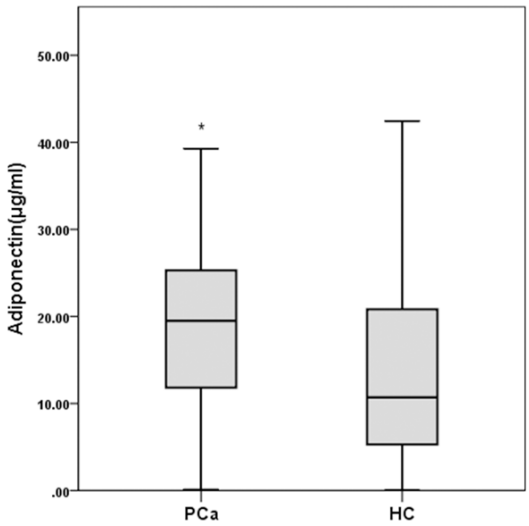

Figure 1. The adiponectin levels of PCa patients and healthy control people (n=92 for each group).

methods by a clinical chemistry analyzer (Shimadzu, cl8000, Japan).

Serum adiponectin and leptin concentration determination

Concentrations of adiponectin and leptin were detected in serum samples reserved using an enzyme-linked immunosorbent assay (ELISA) according to the user manual (adiponectin: Cusabio, CSB-E07270h, China; leptin: Cusabio, CSB-E04649h, China). The linear ranges of the assay were 1.562 ng/mL-100 ng/mL for adiponectin and 0.156 ng/mL-10 ng/mL for leptin. The inter-assay and intra-assay coefficients of variation were less than 8% and 10%, respectively.

Statistical analysis

IBM SPSS Statistics for Windows version 20 (IBM Corp, Armonk, NY, USA) was used for statistical analyses. A two-otailed *P*<0.05 was considered as significant for all analyses. Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether they were normally distributed. Quantitative characteristics were reported as mean ± standard deviation (SD). If they were normally-distributed variables, the t-test was introduced for comparison within the group and between groups; if not, we selected the nonparametric Wilcoxon Mann-Whitney test to assess the significant differences between different groups. Subsequently, Spearman's correlation analyses were conducted to test for associations between the level of adipokines and general clinical characteristics and biochemical parameters. Non-parametric Kruskal-Wallis test was used to explore the associations between PCa grades and circulating levels of the adipokines. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the sensitivity and specificity of adiponectin and leptin in the prediction of malignancy and to differentiated cancer patients from the healthy individuals.

Results

The general characteristics including anthropometric measurements and biochemical parameters of patients with PCa (92 subjects) compared with the healthy control group (92 subjects) were listed in **Table 1**. No significant differences were observed in age and BMI between the PCa patients and the healthy controls (*P*>0.05). In addition, we did not find sta-

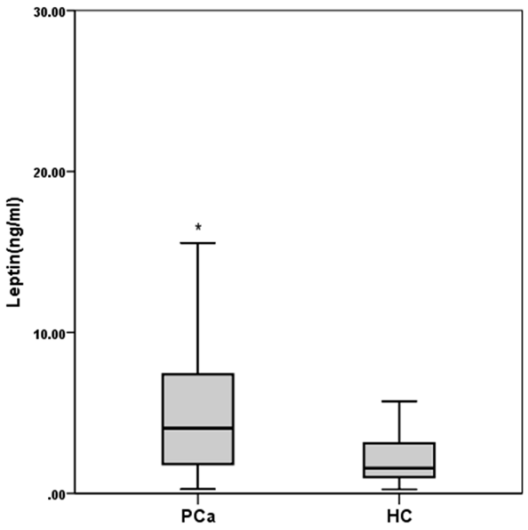

Figure 2. The leptin levels of PCa patients and healthy control people (n=92 for each group).

tistically significant differences in FBG, LDL-C, TC, TG, CRE and BUN levels between PCa patients and healthy controls (P>0.05). Patients with PCa had a higher level of PSA (P<0.001) and HDL-C (P=0.030) than healthy individuals. The adiponectin and leptin levels in both groups were shown in **Table 1**. PCa patients had significantly higher serum adiponectin (P<0.001) and leptin (P<0.001) levels compared with the healthy controls (**Figures 1**, **2**).

Spearman's correlation analyses of adiponectin and leptin levels with clinical and biochemical parameters

Then, we analyzed the correlation between the serum adiponectin and leptin levels with various clinical characteristics and biochemical parameters in PCa group, healthy control group and whole group respectively via Spearman's rank correlation coefficient analysis. The result showed that serum levels of adiponectin was not significantly correlated with age, BMI, serum FBG, HDL-C, LDL-C, TC, TG, CRE, and BUN levels in each group (**Table 2**). Whereas, adiponectin correlated positively with PSA (r= 0.282, P<0.001) in the whole group (**Table 2**). For leptin, we found a positive correlation between leptin and BMI (r=0.269, P<0.001), TG (r=0.205, P=0.005), PSA (r=0.335, P< 0.001) in the whole group. We also found a positive association between leptin and BMI (r=0.461, P<0.001), and FBG (0.345, P=0.001) in healthy control group (**Table 3**).

Associations between adiponectin and leptin levels with grades

We have demonstrated no significant correlation between serum adiponectin levels with PCa grades (χ^2=0.047, P=0.964) (**Table 4**). We also found no significant association between circulating leptin levels with grades (χ^2=1.407, p=0.495) in PCa patients (**Table 5**).

ROC curve of adiponectin and leptin in PCa patients and healthy controls

We showed the ROC curves of the investigated serum adiponectin in **Figure 3**, Using a cutoff point of 8.28 μg/mL for serum levels of adiponectin, we were able to differentiate patients with PCa patients from healthy controls with a sensitivity of 87%, specificity of 56%. In **Figure 4**, leptin serum levels differentiated PCa patients from the healthy controls with a sensitivity of 69%, specificity of 68%, using a cutoff point of 2.40 ng/mL.

Discussion

Prostate cancer (PCa) is the most common urological cancer, which accounts for more than 20% of men's malignant neoplasms. There has been a gradual increase in the frequencies of PCa and obesity in developed countries, with increasingly western eating habits represented by high fat and high cholesterol [23]. Therefore, the parallel morbidity trends of PCa and obesity indicated the possible relevance between them. However, the association between obesity and PCa incidence is complex and has yielded inconsistent conclusions. Park et al. reported that obesity was associated with a higher risk of PCa detection as an independent factor [24], which was supported by several other studies [25, 26]. Among them, Barrington et al. elucidated that obesity was more strongly associated with increased PCa risk among African American than non-Hispanic white men and reducing obesity among African American men could reduce the racial disparity in cancer incidence [25]. Moreover, previous meta-analysis reported associations between a higher BMI and a higher risk of PCa [27]. Conversely, a large age-matched case-control study revealed that elevated BMI was associated with a lower risk of PCa [28]. And interestingly, there were also some other studies argued that BMI was not associated with the risk of PCa [29-31].

Table 2. Spearman's correlation analysis of adiponectin levels with clinical parameters and biochemical parameters

Variables	Prostate cancer group		Normal control group		Whole group	
	Correlation coefficient (*r*)	*P* value	Correlation coefficient (*r*)	*P* value	Correlation coefficient (*r*)	*P* value
Age (years)	-0.182	0.082	-0.151	0.150	-0.103	0.164
BMI (kg/m^2)	-0.170	0.105	0.132	0.210	-0.143	0.052
PSA (ng/mL)	0.136	0.196	0.084	0.424	0.285	**<0.001**
FBG (mmol/L)	-0.163	0.121	-0.025	0.814	-0.096	0.193
HDL-C (mmol/L)	0.079	0.457	0.029	0.782	0.096	0.193
LDL-C (mmol/L)	-0.028	0.788	0.046	0.666	0.055	0.458
TC (mmol/L)	0.171	0.103	-0.048	0.651	0.036	0.629
TG (mmol/L)	-0.083	0.434	-0.004	0.969	0.028	0.784
CRE (μmol/L)	-0.039	0.715	-0.146	0.164	-0.100	0.178
BUN (mmol/L)	0.000	0.997	0.076	0.473	0.072	0.334

Bold values are statistically significant P<0.05. Abbreviations: BMI body mass index, PSA prostate-specific antigen, FBG fasting blood glucose, HDL-C high density lipoprotein-cholesterol, LDL-C low density lipoprotein-cholesterol, TC total cholesterol, TG triacylglycerol, CRE creatinine, BUN blood urea nitrogen.

Table 3. Spearman's correlation analysis of leptin levels with clinical parameters and biochemical parameters

Variables	Prostate cancer group		Normal control group		Whole group	
	Correlation coefficient (*r*)	*P* value	Correlation coefficient (*r*)	*P* value	Correlation coefficient (*r*)	*P* value
Age (years)	0.187	0.075	0.047	0.658	0.183	0.013
BMI (kg/m^2)	0.189	0.071	0.401	**<0.001**	0.270	**<0.001**
PSA (ng/mL)	0.176	0.093	-0.116	0.273	0.348	**<0.001**
FBG (mmol/L)	0.041	0.699	0.346	**0.001**	0.144	0.050
HDL-C (mmol/L)	0.009	0.934	-0.088	0.402	0.015	0.845
LDL-C (mmol/L)	0.061	0.564	-0.073	0.489	0.046	0.536
TC (mmol/L)	0.069	0.512	-0.066	0.534	-0.030	0.686
TG (mmol/L)	0.078	0.459	0.103	0.329	0.170	**0.021**
CRE (μmol/L)	0.078	0.462	0.083	0.430	0.086	0.243
BUN (mmol/L)	0.069	0.512	0.027	0.795	0.093	0.211

Bold values are statistically significant P<0.05. Abbreviations: BMI body mass index, PSA prostate-specific antigen, FBG fasting blood glucose, HDL-C high density lipoprotein-cholesterol, LDL-C low density lipoprotein-cholesterol, TC total cholesterol, TG triacylglycerol, CRE creatinine, BUN blood urea nitrogen.

Table 4. Non-parametric Kruskal-Wallis test on adiponectin levels with PCa status

PCa Grades	N	Mean rank	χ^2	*P* value
Low (Gleason<7)	27	1.96	0.047	0.964
Intermediate (Gleason=7)	29	2.04		
High (Gleason>7)	36	2.00		

Among the different hypothesis that described the relationship between obesity and tumor development, the impact of adipokines on carcinogenesis has been widely discussed. Abnormal synthesis of adipokines such as omentin-1, resistin, apelin, adiponectin and leptin, results in chronic low-grade inflammation in the microenvironment, which may contribute to tumor initiation or progression [11, 32]. For instance, it was showed that omentin-1 significantly inhibited the proliferation of hepatocellular carcinoma cells by inducing apoptosis in these cells [33].

Adiponectin is synthesized in white adipose tissue and exerts function of anti-atherosclerosis, anti-inflammation or anti-insulin resistance [15]. Adiponectin is involved in glucose and lipid homeostasis and is therefore implicated

Table 5. Non-parametric Kruskal-Wallis test on leptin levels with PCa status

PCa Grades	N	Mean rank	χ^2	*P* value
Low (Gleason<7)	27	1.81	1.407	0.495
Intermediate (Gleason=7)	29	2.07		
High (Gleason>7)	36	2.11		

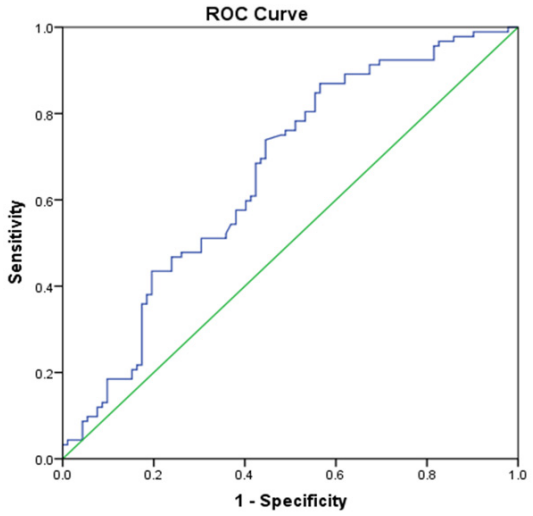

Figure 3. Receiver operation characteristic (ROC) Curve of adiponectin in PCa patients and Healthy controls.

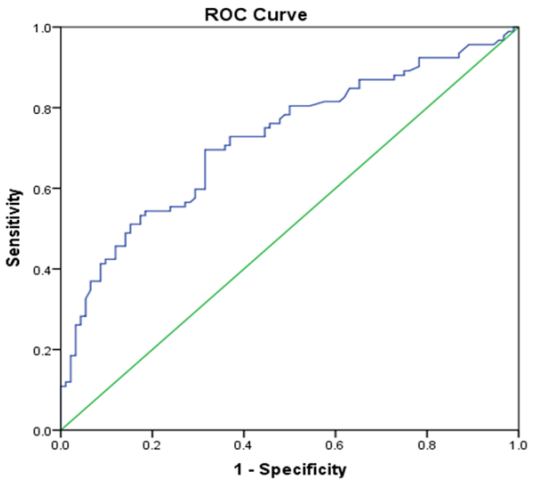

Figure 4. Receiver operation characteristic (ROC) Curve of leptin in PCa patients and Healthy controls.

in the pathogenesis of insulin resistance and diabetes [34]. Altered concentrations of adiponectin have been reported in PCa patients. Although some of these studies reported that cancer patients had significantly lower adiponectin levels than controls [35-37], some other studies did not find any difference in concentrations of adiponectin between patients and controls [33, 38]. Our study demonstrated that patients with PCa had a higher level of adiponectin than healthy controls in Chinese population, which was supported by Al Khaldi et al. [39]. In addition, it has been shown that low adiponectin levels were related to high colorectal cancer risk [40]. Also, some reported circulated levels of adiponectin were inversely correlated with renal cancer incidence [41]. In PCa, Michalakis et al. reported an inverse relationship between adiponectin levels and risk of PCa in an epidemiological study [36], which was supported by another study [42]. However, there were other studies demonstrated that adiponectin concentrations were not associated with risk of prostate cancer [38]. In our study, the circulating adiponectin levels of 20.32±12.09 μg/mL were obviously higher within PCa patients than the healthy people of 14.56±11.72 μg/mL (P<0.05). In addition, we found no correlation between the adiponectin level and PCa grades, indicating that adiponectin might not be associated with the histological grade and disease stage.

Leptin is a kind of peptide hormone which is secreted from adipose tissue in proportion to an individual's fat mass and exerts its effects via blood circulation with targets such as the central nervous system, muscle, liver and adipose tissue [43]. Similar to adiponectin, the leptin concentrations were correlated with obesity and altered concentrations of leptin have been reported in cancer patients. Epidemiological studies indicated increased circulating levels of leptin, as occurs during obesity, were associated with cancers, such as breast and colorectal cancer [19]. Research suggested that leptin played a role in the progression of mammary tissue tumorigenesis via its function as a growth hormone [18]. In addition, leptin had also been studied in vitro on cancer cells and was concerned with proliferation of ovarian, breast, lung pancreatic, and colorectal cancers [22], indicating a crucial effect of leptin in cancer development. In prostate cancer, serum leptin was reported significantly higher in patients with prostate cancer as compared to controls [44], which was supported by other studies [13]. Another study reported although mean serum levels of leptin in case patients

were 10% higher than those in control subjects, the difference was not statistically significant [38]. However, studies reported no significant association between plasma leptin levels and PCa risk was found [38, 45, 46]. Interestingly, there were also studies reported that PCa was associated with raised serum leptin, which was independent of obesity and serum PSA [44]. In our study, the leptin level in PCa patients at 6.28±7.28 ng/ml was higher than healthy controls at 2.44±2.52 ng/ml ($p<0.001$). Furthermore, the serum levels were not correlated with different clinical and biochemical parameters, such as age, FBG, HDL-C, HDL-C, TC, CRE and BUN. In addition, the serum levels were positively associated with BMI and PSA, suggesting leptin may be a marker of PCa related to BMI. Thus, obesity-related leptin exhibits a tumorigenic role in prostate cancer. Similar to adiponectin, we also did not find a correlation between the leptin level and PCa grades, suggesting that leptin also might not be correlated with the histological grades and stages of PCa.

ROC analysis is a standard methodology to evaluate the performance of a classification system, which is applied extensively within clinical medicine. The ROC curve is a two-dimensional plot which illustrates the relationship between the true positive rate (sensitivity) and the false positive rate (1-specificity) of a binary classifier [47-49]. In our study, ROC analysis of the investigated serum adiponectin differentiated cancer patients from the healthy individuals with a sensitivity of 87%, specificity of 56%; leptin levels also distinguished patients from healthy controls with a sensitivity of 69%, specificity of 68%, indicating the diagnostic role of the adipokines.

In conclusion, we found significantly elevated adiponectin and leptin levels in patients with PCa, which were independent of most of the clinical and biochemical parameters. Adiponectin and leptin may be important markers of PCa. In the future, more large cohort-based researches will be necessary to elucidate the possible mechanisms underlying the deregulated adipokines levels and the interactions between adipose tissues with PCa. Such efforts will shed novel insights into effective and efficient therapy and diagnosis of prostate cancer.

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Disclosure of conflict of interest

None.

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