Original Article

The correlation between vascular endothelial growth factor and prostate cancer with and without metabolic syndrome

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Abstract

Objective: To investigate the relationship between vascular endothelial growth factor (VEGF), metabolic syndrome and its components and degree of differentiation of prostate cancer.

Methods: The clinical data of 49 PCa cases treated during October, 2018 to February, 2021 were retrospectively analyzed, including patients' height, weight, body mass index (BMI), age, blood pressure (BP), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), vascular endothelial growth factor (VEGF) and Gleason score.

Results: Compared with simple PCa group, BMI, the MS group had higher BMI, diastolic blood pressure (DBP, FGB, TG) and VEGF ($P<0.05$), and higher Gleason score ($P<0.05$). MS group had a higher degree of malignancy (Gleason≥8).

Conclusion: This suggests that MS may promote the progression of PCa, and the increase of VEGF level can indicate the presence of MS in PCa patients, reflecting the progression of PCa to a certain extent.

Key words: metabolic syndrome, metabolic components, vascular endothelial growth factor, prostate cancer, Gleason score.

Introduction

Prostate cancer (PCa) is one of the male malignancies with the highest incidence in Western countries. In United States, the number of new PCa in 2019 is about 170,000, ranking second only to lung cancer.[1, 2] In recent years, the incidence of PCa in China has gradually increased, ranking the 3rd among male urogenital malignancies. Metastasis of PCa mainly depends on blood vessels and lymphatics, and the late detection and poor prognosis of patients are the main reasons for the high mortality.[1] Relevant immigration epidemiological studies have found that the incidence of PCa among Asian people in the United States is as high as 77.8 per 100,000, which is similar to that of local residents and significantly higher than that of Asian people. This suggests that, in addition to age, race and family history;changes in diets and lifestyles in China and the West may play an important role in the occurrence and progression of PCa.[3] And the metabolic syndrome (MS) to a certain extent, reflects the diet and lifestyle of patients. In addition, Vascular endothelial growth factor (VEGF) as a kind of multi functional cytokine, is closely related to tumorigenesis and metastasis. Many recent studies have shown that VEGF is closely related to the occurrence and development of PCa and MS.4 This study mainly discussed the relationship between various components of MS and VEGF level and the differentiation of PCa.

Materials and Methods

1.1 General data A total of 49 patients with PCa confirmed by pathological findings admitted to our hospital from October 2018 to February 2021 were analyzed. Among them, 12 patients with

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PCa with concomitant MS were in the observation group with an average age of (69.41±6.52) years. They were the observation group. The mean age of 37 patients of PCa without MS were (71.29+7.65) years, and they were the control group. Clinical data of two groups of patients were analyzed retrospectively.

1.2 Diagnosis of metabolic syndrome

The diagnosis of MS was based on the criteria defined by the World Health Organization for the comprehensive metabolic syndrome: 5(1) body mass index (BMI)>25 kg/m^2; (2)blood pressure (BP)>130/85mmHg; (3) fasting triglyceride (TG) ≥1.7mmol/L (150mg/ dL); (4)High density lipoprotein cholesterol (HDL-C)<40 mg / dl (male) or 50 mg/dl(female); (5)Fasting blood glucose (FBG) > 5.6 mmol/L. If three or more of them are met, the diagnosis of MS is made. Exclusion criteria:(1) long-term use of drugs that affect blood glucose, blood lipid, blood pressure and related metabolism (patients with clear diagnosis of diabetes, hyperlipidemia and hypertension were not included in the exclusion criteria); (2) Use of hormone drugs in last 1 month; (3) Acute prostatitis and other urinary tract infections; (4) Endocrine therapy, radiotherapy and chemotherapy; (5) have serious heart, lung, liver, kidney and other diseases; (6) severe psychiatric illnesses; (7) patients with other tumor diseases.

1.3 The research methods: PCa observation indexes, VEGF and clinical biochemical metabolic indexes were measured: height was measured by calibrated height meter (excluding shoes), weight was measured by calibrated scale (excluding overcoat and other heavy objects), and the calculated fractions of BMI were BMI = weight (kg)/ height^2 (m^2).Blood pressure was measured by calibrated sphygmomanometer according to indirect measurement method.The levels of FBG and TG were determined by enzymatic method, the level of HDL-C was determined by chemical precipitation method, and the content of VEGF in human serum was determined by chemiluminescence method using automatic biochemical analyzer.

1.4 Statistical method: SPSS25.0 statistical software was used for statistical processing. The study data were normally distributed, the measured data were expressed as `x±s, X2 test was performed for the counting data between the two groups, and t test was performed in the measurement data. (P<0.05) indicates that the difference is statistically significant.

2 Results

2.1 Clinical characteristics of 49 patients with PCa: Statistical analysis showed (Table 1, 2) that there was no significant difference in age and systolic blood pressure (SBP) between PCa without MS group and PCa with MS group (P>0.05).BMI, diastolic blood pressure (DBP), TG, HDL-C, FBG and Gleason score had statistically significant differences (P>0.05). BMI, DBP, TG, FBG and VEGF in PCa with MS group were higher than those in simple PCa group, while the level of HDL-C was lower than that in PCa without MS group, and PCa with MS group had higher Gleason score (Gleason score≥8) than that in simple PCa group.

Table 1 T-test for clinical data comparison between PCa patients with MS and without MS.

PCa without MS	PCa with MS	t	P	
age	71.29±7.65	70.17±6.35	0.462	0.646
BMI	22.54 + 2.72	27.51±3.09	5.312	0.001
SBP (mmHg)	133.37 + 13.01	143.58±12.58	2.378	2.727
DBP (mmHg)	75.44 + 10. 08	84.50+9.24	2.787	0.007
TG (mmol/L)	1.07±0.48	2.01±1. 00	3.145	0.008
HDL-C (mmol/L)	1.20±0.29	0.85±0.20	4.678	0.001
FBG (mmol/L)	5.07±1.02	6.57±2.05	3.367	0.002
VEGF (pg/ml)	84.68±53.86	146.61±47.26	3.558	0.001

Table 2 Gleason score comparison between PCa patients with MS and without MS

PCa	PCa with MS	X2	P	
Gleason score			4.305	0.037
<8	22(59.4)	3(25)		
≥8	15(40.5)	9(75)		

2.2 VEGF scores between the two groups In the group of PCa with MS patients, there was no significant difference in VEGF level between FBG and DBP groups (P>0.05).There were statistically significant differences in VEGF levels between the BMI, HDL-C and TG groups (P<0.05).The higher VEGF level, the higher BMI and TG, and the lower HDL-C level (P<0.05).However, among the MS components, only the BMI group had statistical significance in Gleason score index (P<0.05), while TG, HDLC, FGB and DBP groups had no statistical significance in Gleason score index (P>0.05).It

can be considered that there is no difference in Gleason score level between the three groups (Tables 3 and 4).

Table 3 Comparison of Gleason score and MS components

MS components		Gleason score	X2	P	
	<8	≥8		4.737	0.029
BMI (kg/m^2)	≤25	18	18		
	>25	2	11	0.047	0.827
HDLC(mmol/L)	<1.03	5	5		
	≥1.03	18	21		
FGB(mmol/L)	<5.6	14	19	0.827	0.363
	≥5. 6	9	7		
TG(mmol/L)	<1.7	6	4	0.860	0.353
	≥1.7	17	22		
DBP(mmHg)	<85	16	23	0.003	0.953
	≥85	4	6		

Table 4 Comparison of VEGF and MS components

MS components		VEGF(pg/ml)	t	P
BMI (kg/m^2)	≤25	89.86±58.76	6. 159	0. 010
	>25	127.48±49.51		
HDLC(mmol/L)	<1.03	140.60±66.23	2.619	0.011
	≥1.03	89.39±52.17		
FGB(mmol/L)	<5.6	88.62±57.00	1.989	0.052
	≥5. 6	122.99±56.03		
TG(mmol/L)	<1.7	86.806±50.436	3.409	0.001
	≥1.7	150.689±62.042		
DBP(mmHg)	<85	94.700±59.717	1.223	0.227
	≥85	119.90±50.794		

Discussion

MS is a metabolic syndrome consists of obesity, elevated blood pressure, elevated blood glucose and dyslipidemia as the main changes, reflecting the diet and lifestyle of patients to a certain extent. Most studies have proved that MS is a high-risk factor for cardiovascular diseases and some cancers.[6] Epidemiological studies have shown a correlation between geography and PCa risk, with the incidence of PCa actually 15 times higher in Western men than in Asian men. This suggests that environmental factors or lifestyle, especially eating and nutrition, may play a key role in the development of PCa.[7] However, the relationship between MS and PCa has not been clearly confirmed, and the results of numerous experimental papers are widely different. Among the confirmed conclusions, hyperlipidemia and obesity component of MS are associated with an increased prevalence of PCa.[8]

In this study, it was found that more than 20% of the patients diagnosed with PCa were complicated with MS, and PCa patients with MS had higher Gleason score and VEGF level than patients with PCa without MS. This suggests that MS plays a promoting role in the progression of PCa, and VEGF plays a contributory role in the progression of PCa and the process of PCa with MS. There was no statistical difference in age and systolic blood pressure between the two groups. The clinical value of VEGF in the diagnosis of PCa patients still needs to be explored.[9] Peyromaure et. al, analyzed 47 patients who underwent needle biopsy for suspected PCa. There were 27 malignant cases (22 localized cancers) and 20 benign cases, and there was no significant difference in VEGF levels between the two groups (69.5pg/ml and 55pg/ml, P=0.55). VEGF indicates prognosis in PCa patients.[10] A study found that the higher Gleason score, the higher clinical stage, and the higher VEGF expression in PCa patients, presenting a positive correlation. The expression of VEGF was not correlated with age, smoking, bone metastasis, seminal vesicle infiltration, and positive surgical margin.VEGF plays a suggestive role in the progression of PCa with MS.Marcin Barylski.[11] studied the expression of VEGF in serum of MS patients and showed that the level of VEGF to be decreased.In China, Li Jianzhi et al.[12] studied the increase of VEGF level in rabbit atherosclerosis model by immunohistochemical method.In this study, the changes of VEGF in the metabolism of PCa patients were studied. VEGF was positively correlated with BMI and TG of PCa patients, while negatively correlated with HDLC.

The differences of BMI components in Gleason score and VEGF level were statistically significant. Patients with BMI≥25 had higher Gleason score and VEGF level ($P < 0.05$).This is similar to the results of known studies.Meta-analysis showed that every 5 kg/m2 increase in BMI in PCa patients was associated with a 15% increase in mortality. Obesity can increase the risk of PCa, reduce the incidence of low-grade PCa, and increase the incidence of high-grade PCa, and worse prognosis.[13]

Insulin resistance and hyperinsulinemia are the pathophysiological basis of MS.Insulin disorders and insulin-like growth factor (IGF) levels were increased in MS patients.[14] IGF can cooperate with DHT to promote the proliferation of prostate epithelial cells, thus playing an important role in the regulation of prostate growth and function.[15] Some studies found that obese men with elevated C-peptide had a 2.66-fold increased risk ratio for PCa-specific death. And PCa patients with high blood sugar have a higher risk of recurrence after treatment. Previous studies have shown that high insulin levels can promote the occurrence and mortality of high-grade PCa.In this study, there was no statistical difference in Gleason score between PCa patients with abnormal fasting blood glucose (FGB≥8) and PCa patients without MS, and the difference in results may be related to long-term oral metformin drugs, which have been proven to reduce the risk of tumor incidence and death.[16]

High TG and low HDL-C are risk factors for PCa.[17] In this study, there was no significant difference in Gleason score between the high TG group and the low HDL-C group and the normal group, suggesting that the level of blood lipid had no significant effect on the progression of PCa. This is inconsistent with the relevant research results.[13] Some scholars believe that the occurrence of PCa will lead to the decrease of TG and HDL-C levels,[18] and the disorder of blood lipid is not the cause of PCa, but its result. In some trials, TG was associated with a higher risk of PCa. The pathogenesis includes fat-induced changes in the hormonal environment, induction of oxidative responses, or high levels of insulin-like growth factor. These can promote the growth of PCa cells in the body.[19] At the same time, considering the dietary structure of the local population and other factors, it should be acknowledged that the existing research results may have potential bias. Some relevant studies have suggested that hypertension and hypercholesterolemia can promote PCa in the advanced stage.20 This study showed that the PCa group combined with MS and the PCa group alone only had statistical significance in the comparison of diastolic blood pressure, and diastolic blood pressure had no correlation with Gleason score and serum VEGF level. It is suggested that blood pressure does not play a significant role in the progression of PCa, which is inconsistent with the existing conclusions. This apparent difference could be attributed to a number of confounding factors, such as study size, demographic and anthropometric characteristics. Considering the eating habits of the local population with high salt and high fat, and the small sample size, further study with large sample size is needed.

Many studies have shown that as the number of MS components increase, PCa Gleason score is higher, the malignant degree of tumor is higher, its prognosis is poorer, mortality is higher. It was believed that a single parameter of MS could not determine the risk of PCa, and only the combined presence of several parameters could increase the risk of development of PCa.[6,21]

The higher degree of malignancy in PCa patients with MS can be attributed to the following reasons: (1)Insulin resistance leads to high insulin and IGF levels in the body, thus promoting the progression of PCa. (2)An important component of MS is obesity. Excessive adipocytes in MS patients can synthesize and secrete inflammatory factors such as interleukin-6, which act on target organs through autocrine, paracrine and endocrine pathways, some of which are involved in the occurrence and progress of PCa. In addition, MS can cause chronic inflammatory state in the body, increase the level of pro-inflammatory factors in the body, and form a tumor-promoting micro environment. The increase of pro-inflammatory cytokines TNF- A, interleukin-6 and IL-8 in MS patients can activate the NF- kB pathway, thus affecting the progression and prognosis of tumors. VEGF has a powerful effect of enhancing vascular permeability and participating in the inflammatory response, and its changes suggest the process of PCa.

At present our study has some limitations: first of all, because the object of this experiment has patients in Chengde, Hebei Province, China. The experimental data was small. Considering that the local diet was dominated by high-fat and high-sodium diet, the diagnosis of MS was affected to a certain extent. In addition, the subjects in this study did not have regular physical examination before PCa was initially confirmed by pathology, which may affect the

statistical analysis results and have potential bias. Secondly, some confecting factors also interfered with the statistical accuracy, such as the local population's high-salt and high-fat dietary habits, the patient's family history, metformin, statins, alpha blockers and other drugs that can affect the diagnosis of MS or PCa. In addition, this study is a retrospective analysis, which may affect the analysis results of blood pressure, blood glucose and blood lipids. In addition, retrospective analysis can only analyze and evaluate whether there is a relationship between the three. Such causal conclusion is limited. Finally, most of the pathological data came from prostate puncture, not all from radical prostatectomy specimens. Therefore, more in-depth laboratory and a large number of epidemiological studies are needed to understand the influence of MS on the progression of PCa and the relationship between VEGF and PCa combined with MS, so that we can better regulate daily life and diet and provide help for the clinical treatment of PCa.

In conclusion, the results of this study showed that BMI, DBP, TG and FGB were all correlated with the incidence of PCa, and the malignant degree of PCa patients with three or more abnormalities was higher (Gleason score≥8), suggesting that MS promoted the progression of PCa. Moreover, the increase of serum VEGF level can indicate the complication of MS in PCa patients, reflecting the progress of PCa to a certain extent. The object of this study is limited to Chengde area, and further studies should be conducted in different areas and different populations in the future, so as to better provide reference prevention or treatment for PCa patients with MS.

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