Int J Clin Exp Med 2016;9(9):18500-18506
www.ijcem.com /ISSN:1940-5901/IJCEM0031260

Original Article

Metabolic syndrome components were related to the risks of prostate cancer

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Received April 26, 2016; Accepted August 4, 2016; Epub September 15, 2016; Published September 30, 2016

Abstract: Our study is to investigate the relationships between the metabolic syndrome (MS) components and the risks of the prostate cancer (PCa) in Chinese Han male population. We studied 186 PCa patients with or without MS and 107 healthy controls. Clinical data including age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TCHO), high density lipoprotein (HDL), low density lipoprotein (LDL) and other related indicators were collected. The relationships between cases of PCa and controls were analyzed by t-test. The relationships between high-risk cases, low-risk cases and controls were analyzed by the analysis of variance (ANOVA) and ordinal logistic regression with SPSS 18.0. The age, BMI, DBP, TCHO and HDL were statistically significant between PCa patients and controls ($P<0.05$), but the age, DBP, TG, TCHO and HDL were statistically significant between high-risk cases, low-risk cases of PCa and controls these three groups ($P<0.05$). Among them, the age and TCHO were statistically significant not only between high-risk cases and controls but also between low-risk cases and controls. The DBP and HDL were statistically significant between high-risk cases and controls only. As mentioned, BMI is statistically significant between PCa cases and controls, but it is not statistically significant between high-risk cases, low-risk cases and controls these three groups and TG is just the opposite. It means that BMI is associated with the risks of PCa occurrence, which is not associated with high or low risks of occurred PCa. TG is associated with the high-risk of occurred PCa, which is not with the risks of PCa occurrence. The age, DBP, TCHO and HDL were associated with the risks of PCa occurrence and the degree of occurred PCa risks. BMI is associated with the risks of PCa occurrence and TG is associated with the high-risk of occurred PCa only.

Keywords: Metabolic syndrome components, prostate cancer risks

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer and the sixth cause of cancer-death worldwide [1]. It is estimated that 1.6 million new cases of PCa were diagnosed and 500 thousand patients died of this disease in 2015 [2].

Metabolic syndrome (MS) which has become a major public health problem, is a disorder of energy utilization and storage [3]. The WHO definition of the MS is glucose intolerance, impaired fasting glucose, diabetes or insulin resistance, which plus at least two of the following criteria: ① waist-to-hip ratio of >0.90 in men and >0.85 in women; ② Serum TG>150 mg/dL (1.7 mmol/L); ③ HDL<35 mg/dL (0.9 mmol/L) in men and <39 mg/dL (1.0 mmol/L) in women; ④ Blood Pressure >140/90 mmHg; ⑤ Urinary albumin excretion rate >20 ug/min or albumin: creatinine ratio >30 mg/g [4].

The association between MS components and PCa development has not been studied comprehensively and published studies about the topic reported divergent results. Tande AJ. found that MS components were associated with a decreased PCa incidence [5], but Lund Håheim L. found that MS may increase PCa incidence by an association between insulin resistance and incidence of PCa [6].

Among the studies that have considered MS and its components, some have found a positive association in Scandinavians [7] and Afro-Americans [8, 9], whereas others have found an inverse association in Scandinavians or whites

Table 1. The metabolic characteristics of cases and controls

	Cases		Controls		t	P
	n	$\bar{x} \pm s$	n	$\bar{x} \pm s$		
Age	186	76.67±7.598	107	69.17±8.259	7.707	<0.001
Height	61	170.23±4.870	101	169.76±5.450	0.565	0.573
Weigh	184	71.11±11.552	106	73.46±8.729	-1.816	0.070
BMI	61	24.48±3.861	101	25.67±3.040	-2.057	0.042
SBP	186	140.45±18.701	105	147.09±84.024	-1.034	0.302
DBP	186	79.63±11.657	105	85.38±13.022	-3.756	<0.001
FBG	177	5.78±1.795	90	6.00±1.311	-1.126	0.261
TG	95	1.28±0.635	84	1.58±0.952	-2.534	0.012
TCHO	96	4.58±0.993	84	5.72±1.185	-6.918	<0.001
HDL	92	1.24±0.298	83	1.37±0.265	-2.886	0.004
LDL	93	2.74±0.658	83	2.58±0.614	1.669	0.097

in the USA [10, 11]. Moreover, Martin RM found little evidence to support the hypothesis that the MS or its components explain higher PCa mortality rates [12].

In order to specifically address this issue, our study investigated the underlying associations of MS components with PCa development and progression in prevention and treatment of PCa.

Materials and methods

Ethics statement

This study was approved by the Ethics Committee of the Second Hospital of Shandong University. Each eligible patient wrote the informed consent according to the Declaration of Helsinki.

Study subjects and inclusive and exclusive criteria

We admitted PCa patients who were Han individuals without other malignancies, hepatorenal dysfunction and family history of PCa. Individuals with long-term administration of drugs which effect on blood lipids, blood pressure or related metabolism were excluded. On the other hand, the controls with no dysuria or abnormity examined by anus touch or B-ultrasound, whose PSA was less than 4 ng/ml, were admitted. This study was carried out between July 2013 and July 2015 in a population of male patients (n=186) with pathological confirmed PCa and healthy controls (n=107) finally admitted to the Qilu and Second hospital of shandong university, the Shandong-provinced hospital and the Qianfoshan hospital of shandong province. Tumors with a gleason score ≥7 and the stage of TNM ≥II were considered high-risk cases; gleason score <7 and the stage of TNM <II were considered low-risk cases [13].

Data collection

All the data were collected from the hospitals mentioned above. The General information of the subjects, including age, height (cm), weight (kg), BMI, SBP and DBP were recorded. Venous blood was collected and common clinical laboratory indicators, including FBG, TG, TC, LDL and HDL were measured and recorded. All the patients with PCa were confirmed by pathological results and the gleason scores were recorded. Age at biopsy, height, weight, digital rectal examination (DRE), pre-biopsy PSA levels, prostate volume, histopathologic diagnosis after surgery and the gleason scores were collected from all patients.

Statistical analysis

The basic characteristics of cases and controls were analyzed by t-test. The results of the controls, the low-risk and high-risk cases were compared using analysis of variance (ANOVA) for the categorical variables. The relationships between these three groups were analyzed by ordinal logistic regression. All analysis was conducted using SPSS version 18.0 (SPSS Inc., Chicago, Illinois, USA). The *p* values of <0.05 were regarded as statistical significance.

Result

Basic metabolic characteristics of cases and controls

The data collected allowed us to examine the features of the MS components in Chinese Han men population. In this study, two groups involved 293 Chinese Han males, including 186 men with PCa and 107 ones with disease-free controls. From **Table 1**, we find that cases were significantly older than controls (P<0.001).

Table 2. The Characteristics of the controls, the low-risk and the high-risk cases

	Cases				Controls		F	P
	High-risk cases		Low-risk cases					
	n	$\bar{x} \pm s$	n	$\bar{x} \pm s$	n	$\bar{x} \pm s$		
Age	139	(76.69±7.688)[a]	47	(76.63±7.407)[b]	107	(69.17±8.259)[a,b]	30.963	<0.001
BMI	47	24.66±3.89	14	23.87±3.83	101	25.67±3.04	2.668	0.072
SBP	139	139.64±18.34	47	142.85±19.73	105	147.09±84.02	0.598	0.551
DBP	139	(78.94±11.58)[a]	47	81.66±11.76	105	(85.38±13.02)[a]	8.399	<0.001
FBG	133	5.76±1.74	44	5.85±1.97	90	6.00±1.31	0.576	0.563
TG	74	(1.25±0.63)[a]	21	1.39±0.66	84	(1.58±0.95)[a]	3.450	0.034
TCHO	75	(4.70±0.74)[a,b]	21	(4.15±1.56)[a,b]	84	(5.72±1.18)[a,b]	27.088	<0.001
HDL	73	(1.24±0.29)[a]	19	1.23±0.34	83	(1.37±0.27)[a]	4.153	0.017
LDL	74	2.74±0.62	19	2.75±0.81	83	2.58±0.61	1.380	0.254

Note: [a]the P of high-risk cases and controls <0.05; [b]the P of low-risk cases and controls <0.05; [c]the P of high-risk and low-risk Cases <0.05.

Table 3. The ordinal logistic regression result between high-risk, low-risk cases and controls

		Estimate	S.E.	Wald	df	Sig.	OR 95% CI	
							Lower	Upper
Threshold	high-risk	1.102	4.468	0.061	1	0.805	-7.656	9.860
	low-risk	1.737	4.471	0.151	1	0.698	-7.027	10.501
Location	age	-0.108	0.034	9.937	1	0.002	-0.175	-0.041
	BMI	-0.002	0.087	<0.001	1	0.983	-0.172	0.168
	SBP	0.007	0.004	2.262	1	0.133	-0.002	0.015
	DBP	0.067	0.029	5.519	1	0.019	0.011	0.123
	FBG	0.004	0.153	<0.001	1	0.980	-0.297	0.304
	TG	0.610	0.588	1.076	1	0.300	-0.542	1.762
	TCHO	2.024	0.612	10.951	1	<0.001	0.825	3.223
	HDL	0.085	1.482	0.003	1	0.954	-2.820	2.989
	LDL	-2.802	0.808	12.030	1	<0.001	-4.385	-1.219

Logit Link-function: Link1=1.102-(-0.108*age-0.002*BMI+0.007*SBP+0.067*DBP+0.004*FBG+0.610*TG+2.024*TCHO+0.085*HDL-2.802*LDL); Link2=1.737-(-0.108*age-0.002*BMI+0.007*SBP+0.067*DBP+0.004*FBG+0.610*TG+2.024*TCHO+0.085*HDL-2.802*LDL).

In addition, BMI, DBP, TG, TCHO and HDL were statistically significant between cases and controls (P<0.05), which means that cases have less BMI, DBP, TG, TCHO and HDL.

Results of the controls, the low-risk and the high-risk cases

Table 2 summarizes the results regarding to the clinical characteristics of the controls, the low-risk and high-risk cases by ANOVA. The age and TCHO of controls were statistically significant from the low-risk and high-risk cases both (P<0.05), which means that controls have less age and larger TCHO statistically. The DBP, TG and HDL were statistically significant (P<0.05) between controls and high-risk cases without low-risk cases. The association between the high-risk and low-risk cases was analyzed, which presents no statistically significance in all the information.

As mentioned, BMI is statistically significant between PCa cases and controls, but it is not statistically significant between high-risk cases, low-risk cases and controls. It means that BMI is associated with the risks of PCa occurrence, which is not with high or low risks of occurred PCa. TG is statistically significant between high-risk PCa cases and controls, but it is not statistically significant between PCa cases and controls. It means that TG is associated with the high-risk of occurred PCa, which is not with the risks of PCa occurrence.

The ordinal logistic regression result between the high-risk, low-risk cases and controls

Table 3 presents crude and adjusted ORs and 95% CIs for the MS components according to the cases and controls. From **Table 3**, the P of age, DBP and TCHO were less than 0.05 statistically, which means that age, DBP and TCHO

were associated with high-risk and low-risk cases from the controls. However, although the P of LDL was less than 0.001 statistically in **Table 3**, P of ANOVA (P=0.254) of them was larger than 0.05 in the **Table 2**, which means that LDL and other indicators were not associated high-risk and low-risk cases from the controls.

There were two logit link functions under the **Table 3**, which were used to predict the risks of PCa occurrence and the stage of occurred PCa. According to the logit link function and individual indicators, we can get the result of link 1 and link 2. Then we can get the p result and predict the PCa incidence. For example, age=69, BMI=20.77, SBP=121, DBP=67, FBG=4.02, TG=0.62, TCHO=3.96, HDL=0.95, LDL=2.12, Link 1=0.709, Link 2=1.3447. P1=1/(1+Exp(-0.7097))=0.670337, P2=1/(1+Exp(-1.3447))=0.793263, P3=1-(P1+P2)=-0.4636. Because P2 is the largest, the risk of PCa is low.

Discussion

PCa is a chronic disease that exhibits early initiation and slow progression, which is the most frequently diagnosed malignancy in industrialized countries [14]. Epidemiological studies reported that the incidence of PCa in western countries was 10-15 times higher than that of Asian countries [15].

In 1988, Reaven [16] described Syndrome X as a cluster of clinical conditions that serve as risk factors for cardiovascular disease. MS is a cluster of cardiovascular risk factors, including hypertension, diabetes mellitus, obesity, high TG and low HDL, with insulin resistance as the underlying hallmark feature [17].

MS was firstly observed as composite factors associated with PCa risks in 2004 [18]. In 2007, Hsing et al. summarized five studies on MS and PCa risk, concluding that the epidemiologic evidence was insufficient to suggest a link between MS or its components and PCa [19]. Other authors also concluded that MS or its components was not associated with PCa risks [20]. Interestingly, Giovannucci et al. found a quite contrasting result when studying the PCa risk by age using data from the U.S. Health Professionals Follow-up Study: they found a significant inverse association between body mass index (BMI) and PCa risk among men younger than 60 years but a weak positive association among men older than 60 [21].

The relationship between individual components of MS and worse pathological results of PCa has been reported: patients with higher tumor grade and higher disease stage were not more obese or dyslipidemic, who had elevated visceral adipose tissue accumulation and fasting plasma insulin levels [22]. The accumulating impact of MS components on PCa risk and mortality has also been evaluated. An increasing number of MS components was correlated with a higher probability of PCa, as well as higher PCa mortality [23].

We studied prospectively the effects of MS components on the risk of PCa. The MS components were assessed both separately and in clusters. Our main findings were that a cluster of factors related to the MS substantially increased the PCa risk. In our present study, the potential role of MS components in the diagnosis of PCa was further strengthened by the detailed evidence we gathered. As an increasing number of MS components became involved, components analyzed in this study, including BMI, DBP, TG, TCHO and HDL, were statistically less in the Cases Group.

Prostate cancer is rarely diagnosed in men younger than 50 years old, accounting for only 2% of all cases. The median age at diagnosis is 68 years, with 63% diagnosed after age 65. At 85 years of age, the cumulative risk of clinically diagnosed prostate cancer ranges from 0.5% to 20% worldwide, despite autopsy evidence of microscopic lesions in approximately 30% of men in the fourth decade, 50% of men in the sixth decade, and more than 75% of men older than 85 years. In our study, Age at Diagnosis of cases was larger, which is the same with the results before.

In our study, TCHO and HDL were less in the cases groups. In our study, the TCHO and HDL level was statistically less in the Cases group. This hypo-TCHO and HDL may be the result rather than the cause of PCa, since it has already been demonstrated that the presence of cancer can cause decreased levels of this substance [24]. This has been confirmed by several epidemiological studies which demonstrated people with cancer present lower levels of TCHO and HDL with reasons still unknown

[25]. However, the role of TCHO and HDL in the physiopathology of PCa was still controversial. Studies have provided evidence that TCHO and HDL was a mediator of signal transduction processes which were important for PCa tumor cell survival and disease progression [26]. TCHO and HDL was a precursor of androgenic hormones, which interfere directly in the process of genesis and progression of PCa [27].

BMI has been suggested as a risk factor for prostate cancer. Several studies have shown that BMI show significant positive correlation with markers of oxidative stress. Treatment of obesity through reduction in fat intake and increased exercise has been shown to reduce oxidative stress. Three large prospective studies, examining the association between obesity and prostate cancer risk, suggested that high BMI was associated with a lower risk of low-grade disease but a greater risk of high-grade disease. In our study, BMI is associated with the risks of PCa occurrence, which is not with high or low risks of occurred PCa. Potential explanation include the association of obesity with higher serum estradiol, insulin, free IGF-1, and leptin levels, and lower free testosterone and adiponectin levels, which have also been associated with more aggressive prostate cancer. Another explanation is detection bias. Higher BMI has also shown to be associated with low serum PSA, which in high BMI men could lead to fewer biopsies.

Prostate cancer incidence and mortality rates around the world correlate highly with the average level of fat consumption, especially for polyunsaturated fats. In our study, TG is associated with the high-risk of occurred PCa. Potential mechanisms of action include fat-induced changes in the hormonal milieu, induction of oxidative stress, and/or insulin-like growth factor (IGF-1). High levels of dietary fat stimulate proliferation of prostate cancer cells both in vitro and in vivo, and animal models have shown that a fat-free diet can reduce the growth of androgen-dependent tumors in the Dunning model.

There were many different opinions of molecular and cellular mechanism in this field. The precise underlying mechanisms of PCa remain unknown; nevertheless, genetic alterations and the role of metabolic disturbances in the pathogenesis of PCa, including obesity, hyperinsulinemia and insulin resistance, have been demonstrated [28]. In addition, MS has been suggested as a potential risk factor in the pathogenesis of PCa [29].

MS components were associated with a pro-inflammatory state elevated levels of CRP, tumor necrosis factor-a (TNF-a), interleukin-8 (IL-8), IL-6, and IL-1b, which were directly linked with PCa risk [30]. High TCHO levels linked to MS were correlated with increased risk of PCa [31]. Secondly, MS conditions can also alter circulating levels of insulin-like growth factor gene-1 (IGF-1), leptin and adiponectin, all of which were linked to PCa risk [32]. However, Esposito et al. demonstrated that MS was weakly and non-significantly associated with PCa risk, associations of which vary with geographic location [33]. Therefore, the controversial nature of existing data should be acknowledged [34].

On the other hand, among the physio-pathological entities that comprise MS, IGF-I seemed to be the one which was most closely linked with PCa [35]. The hyper-insulinemia observed in patients with MS was the factor responsible for stimulating the production of IGF-I in the liver. This, as a potent mitogenic factor and apoptosis inhibitor, increases the cell turnover, which results in higher susceptibility to malignant transformation of cells. Serum levels of IGF-I higher than 60 ng/ml seem to be associated with an increased risk of development of PCa [36]. Another metabolic pathway possibly may be the increasing in TCHO levels. TCHO was an essential constituent of the cell plasmatic membrane, but when its levels become higher than a critical concentration, it can inhibit cell apoptosis through structures known as lipids rafts, which alter the mechanisms of signal transduction [37].

There were several limitations in our present study. Firstly, the relative smaller inclusion of subjects and lower number of variables might have an influence on the statistical analysis performance, which determines whether there was any correlation between MS components and the risk of PCa in a Chinese Han ethnic population. Secondly, the study designed was similar to a case-control study, which was not as robust as a cohort study. The clinical data were extracted from cross-sectional studies, not longitudinal cohort studies, which might

have a negative effect on the optimization of acquisition parameters such as high DBP, low TG, low TCHO and low HDL. Thirdly, the pathological stage data in some studies were extracted from biopsy not radical prostatectomy specimens. Last but not least, to date, there remain limited studies focusing on this association, although many of the available studies were well designed case-control or longitudinal cohort studies. Therefore, there is an urgent future need to confirm this association and to find potential mechanisms to explain how MS components affect the development or progression of PCa.

Acknowledgements

We acknowledge the work of collecting the date of patients in these hospitals (including Shandong Provinced Hospital, Qianfo Mount Hospital of Shandong Proince, Qilu Hospital of Shandong University). Supported by "Study on risk factors of prostate cancer and establishment of screening model for high risk population", a clinical key project of China's Ministry of Health; "Male disease early screening and minimally invasive technology clinical medicine transformative platform construction and promotion at the local level", a science and technology plan for the people of Shandong province; "Individual treatment strategies research of prostate cancer due to large clinical registered trials", a science and technology development plan of Shandong province in the Key Laboratory for Kidney Regeneration of Shandong province.

Disclosure of conflict of interest

None.

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