Asian Journal of Andrology (2015) 17, 839–844

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ORIGINAL ARTICLE

Prostate Disease

The association between metabolic syndrome and advanced prostate cancer in Chinese patients receiving radical prostatectomy

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The global incidence of metabolic syndrome (MetS) is dramatically increasing. Considerable interest has been devoted to the relationship between MetS and prostate cancer (PCa) risk. However, few studies have examined the association between MetS and PCa progression. This retrospective study consisted of 1016 patients with PCa who received radical prostatectomy. The association between MetS and pathological features was evaluated using logistic regression analysis. Compared with patients without MetS, those with MetS indicated an increased risk of prostatectomy Gleason score (GS) ≥8 (odds ratio [OR] =1.670, 95% confidence interval (CI) 1.096–2.545, *P* = 0.017), and a 1.5-fold increased risk of pT3–4 disease (OR = 1.583, 95% CI 1.106–2.266, *P* = 0.012). The presence of MetS was an independent predictor of lymph node involvement (OR = 1.751, 95% CI 1.038–2.955, *P* = 0.036). Furthermore, as the number of MetS components accumulated, the risk of a GS ≥ 8 increased. The present study indicates a significant association between MetS and advanced PCa. The results need to be evaluated in large-scale prospective cohorts.

Asian Journal of Andrology (2015) **17**, 839–844; doi: 10.4103/1008-682X.148138; published online: 16 January 2015

Keywords: Gleason score; metabolic syndrome; pathology; prostate cancer

INTRODUCTION

Prostate cancer (PCa) is the second most common malignancy among men and ranks as the second leading cause of cancer-related mortality in developed countries.[1] Epidemiological studies report that the incidence of PCa in western countries is 10–15 times higher than that of Asian countries.[2] However, with a change in lifestyle, PCa has become the sixth most common cancer among Chinese men, especially in urban areas.[3] Therefore, although the underlying mechanisms responsible for PCa carcinogenesis are not fully understood, growing evidence suggests that it can be partly explained by western lifestyle factors, for example, excess calorie intake and sedentary living habits.[4,5]

Over the past few decades, metabolic syndrome (MetS) has become a more prevalent global health issue,[6] and is thought to influence PCa etiology. Individual components of MetS, such as obesity, hypertension, diabetes, and dyslipidemia, have each been linked to increased PCa risk.[7–10] A large-scale research project in Scandinavia also found a positive association between MetS and PCa risk.[11] However, only a few studies have investigated the relationship between MetS and pathological features of PCa, and these studies have drawn conflicting conclusions. For instance, Kheterpal *et al.*[12] reported that MetS patients had a higher Gleason score (GS) and higher pathological stage. Another research group also observed a significant association between MetS and higher PCa grade.[13] Conversely, Jeon *et al.*[14] found that the presence of MetS was correlated with decreased risk of high-grade PCa in a Korean population. Given the inconsistency of existing information, as well as tumor heterogeneity in patients of different ethnic backgrounds, the present study was intended to provide additional data on the association between MetS and pathological characteristics of PCa in a Chinese population.

PATIENTS AND METHODS

Study subjects

This retrospective study included 1597 consecutive patients with clinically localized PCa from two clinical centers: the Department of Urology at Fudan University Shanghai Cancer Center from January 2005 to June 2014, and the Department of Urology at the Affiliated Hospital of Qingdao University from January 2011 to June 2014. All patients underwent radical prostatectomy and standard pelvic lymphadenectomy. Patients who received neoadjuvant therapy were not enrolled in the study. In addition, 202 patients were excluded because of missing serum lipid profile data. Finally, clinicopathological information of the total 1016 patients, including age, height, weight, history of hypertension and diabetes, lipid profiles, preoperative prostate-specific antigen (PSA) levels, biopsy GS, clinical stage, prostatectomy GS, and pathological stage, was gathered from medical records and analyzed. The study protocol was approved by the

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Received: 20 August 2014; Revised: 27 September 2014; Accepted: 25 November 2014

Institutional Research Review Boards of the two clinical centers, and written informed consent was acquired from all participants.

Exposure measures

Metabolic syndrome was defined according to the criteria recommended by the Chinese Diabetes Society,[15] which requires that at least three of four of the following standards are met: (1) overweight and obesity – body mass index (BMI) ≥25 kg m^{-2}; (2) hypertension – systolic and diastolic blood pressure ≥ 140 and 90 mmHg, respectively, on three consecutive occasions, or a physician's diagnosis of hypertension; (3) diabetes – fasting glucose ≥ 6.1 mmol l^{-1}, or a physician's diagnosis; (4) hypertriglyceridemia and/or low high-density lipoprotein (HDL) level – serum triglyceride level ≥ 1.7 mmol l^{-1} and/or HDL-cholesterol level < 0.9 mmol l^{-1}.

Statistical analyses

Differences in categorical variables were compared using Chi-squared tests. Unconditional logistic regression analysis was performed to estimate odds ratios (ORs) and 95% confidence intervals (CI). Two-sided $P < 0.05$ were considered statistically significant. SPSS 20.0 software (IBM Corporation, Armonk, NY, USA) was used for statistical analyses.

RESULTS

This study included 1016 patients with newly diagnosed PCa with a median age of 68 years (age range: 41–79 years). The range of preoperative PSA levels was 1.13–303.00 ng ml^{-1} (median: 14.82 ng ml^{-1}). According to the American Joint Committee on Cancer TNM staging system (2002), there were 484, 270, and 262 patients with ≤ cT2a, cT2b, and ≥ cT2c disease, respectively. Postoperative pathological assessments determined that 644 patients had pT2 disease and 372 patients had pT3–4 disease. In addition, lymph node involvement was found in 93 patients. **Table 1** indicates the demographic and clinicopathological characteristics of the patients.

Comparisons of each component of MetS with pathological PCa features are listed in **Table 2**. Diabetes was prevalent in PCa patients with prostatectomy GS ≥ 8, pT3–4 disease, or lymph node involvement. Overweight and dyslipidemia were also associated with worse pathological features of PCa. However, no significant difference in hypertension was observed between patients with different pathological features.

Next, the association between postoperative pathological features and preoperative PSA levels, biopsy GS, clinical stage, and MetS was analyzed using univariate and multivariable logistic regression models, respectively. As shown in **Table 3**, after adjusting

Table 1: Demographic and clinicopathological characteristics of the 1016 PCa patients undergoing radical prostatectomy

Clinicopathological features	*MetS, n (%)*		*P*
	Yes (n=178)	*No (n=838)*	
Age (years)			
<68	108 (60.7)	416 (49.6)	0.007
≥68	70 (39.3)	422 (50.4)	
Smoking status			
Never	110 (61.8)	554 (66.1)	0.272
Ever/current	68 (38.2)	284 (33.9)	
PSA (ng ml^{-1})			
<10	37 (20.8)	268 (32.0)	0.008
10≤ PSA <20	61 (34.3)	271 (32.3)	
≥20	80 (44.9)	299 (35.7)	
Biopsy GS			
≤6	52 (29.2)	278 (33.2)	0.395
7	60 (33.7)	291 (34.7)	
≥8	66 (37.1)	269 (32.1)	
Clinical stage			
≤cT2a	84 (47.2)	400 (47.7)	0.819
cT2b	45 (25.3)	225 (26.8)	
≥cT2c	49 (27.5)	213 (25.5)	
Prostatectomy GS			
≤6	27 (15.2)	157 (18.8)	0.010
7	82 (46.1)	452 (53.9)	
≥8	69 (38.7)	229 (27.3)	
Pathological stage			
pT2	92 (51.7)	552 (65.9)	<0.001
pT3-4	86 (48.3)	286 (34.1)	
Lymph node involvement			
Yes	26 (14.6)	67 (8.0)	0.006
No	152 (85.4)	771 (92.0)	

PCa: prostate cancer; MetS: metabolic syndrome; PSA: prostate-specific antigen; GS: Gleason score

Table 2: Association of individual components of MetS with pathological features of PCa

Variable	*Prostatectomy GS*			*Pathological stage*			*Lymph node involvement*		
	≤7, n (%)	*≥8, n (%)*	*P*	*pT2, n (%)*	*pT3-4, n (%)*	*P*	*Yes, n (%)*	*No, n (%)*	*P*
BMI									
<25	495 (68.9)	184 (61.7)	0.027	424 (65.8)	255 (68.5)	0.377	59 (63.4)	620 (67.2)	0.466
≥25	223 (31.1)	114 (38.3)		220 (34.2)	117 (31.5)		34 (36.6)	303 (32.8)	
Hypertension									
No	494 (68.8)	204 (68.5)	0.914	449 (69.7)	249 (66.9)	0.356	56 (60.2)	642 (69.6)	0.064
Yes	224 (31.2)	94 (31.5)		195 (30.3)	123 (33.1)		37 (39.8)	281 (30.4)	
Diabetes									
No	619 (86.2)	238 (79.9)	0.011	566 (87.9)	291 (78.2)	<0.001	70 (75.3)	787 (85.3)	0.011
Yes	99 (13.8)	60 (20.1)		78 (12.1)	81 (21.8)		23 (24.7)	136 (14.7)	
Hypertriglyceridemia									
No	545 (75.9)	218 (73.2)	0.356	498 (77.3)	265 (71.2)	0.031	36 (38.7)	727 (78.8)	<0.001
Yes	173 (24.1)	80 (26.8)		146 (22.7)	107 (28.8)		57 (61.3)	196 (21.2)	
Low HDL-cholesterol									
No	641 (89.3)	256 (85.9)	0.128	579 (89.9)	318 (85.5)	0.035	82 (88.2)	815 (88.3)	0.971
Yes	77 (10.7)	42 (14.1)		65 (10.1)	54 (14.5)		11 (11.8)	108 (11.7)	

BMI: body mass index; MetS: metabolic syndrome; PCa: prostate cancer; GS: Gleason score; HDL: high-density lipoprotein

Table 3: Logistic regression analyses of the association of MetS with pathological features in PCa patients

Variable	*Prostatectomy GS*					
	≤7, n (%)	*≥8, n (%)*	*Crude OR (95% CI)*	*P*	*Adjusted OR[a] (95% CI)*	*P*
PSA (ng ml^{-1})						
<10	256 (35.7)	49 (16.4)	1	<0.001	1	<0.001
10≤ PSA <20	250 (34.8)	82 (27.5)	1.714 (1.155–2.542)	0.007	1.034 (0.649–1.645)	0.889
≥20	212 (29.5)	167 (56.1)	4.116 (2.852–5.939)	<0.001	2.439 (1.575–3.779)	<0.001
Biopsy GS						
≤6	307 (42.8)	23 (7.7)	1	<0.001	1	<0.001
7	295 (41.1)	56 (18.8)	2.534 (1.520–4.224)	<0.001	2.218 (1.319–3.730)	0.003
≥8	116 (16.1)	219 (73.5)	25.200 (15.597–40.716)	<0.001	22.290 (13.638–36.430)	<0.001
Clinical stage						
≤cT2a	362 (50.4)	122 (40.9)	1	0.001	1	0.151
cT2b	195 (27.2)	75 (25.2)	1.141 (0.815–1.597)	0.441	1.077 (0.714–1.625)	0.724
≥cT2c	161 (22.4)	101 (33.9)	1.861 (1.348–2.570)	<0.001	1.483 (0.988–2.227)	0.057
MetS (no/yes)						
No	609 (84.8)	229 (76.8)	1	0.002	1	0.017
Yes	109 (15.2)	69 (23.2)	1.683 (1.201–2.360)		1.670 (1.096–2.545)	
Variable	*Pathological stage*					
	pT2, n (%)	*pT3–4, n (%)*	*Crude OR (95% CI)*	*P*	*Adjusted OR[a] (95% CI)*	*P*
PSA (ng ml^{-1})						
<10	251 (39.0)	54 (14.5)	1	<0.001	1	<0.001
10≤ PSA <20	219 (34.0)	113 (30.4)	2.398 (1.654–3.477)	<0.001	1.998 (1.356–2.945)	<0.001
≥20	174 (27.0)	205 (55.1)	5.476 (3.833–7.824)	<0.001	4.130 (2.835–6.016)	<0.001
Biopsy GS						
≤6	271 (42.1)	59 (15.9)	1	<0.001	1	<0.001
7	225 (34.9)	126 (33.9)	2.572 (1.801–3.673)	<0.001	2.279 (1.574–3.300)	<0.001
≥8	148 (23.0)	187 (50.2)	5.804 (4.071–8.274)	<0.001	4.490 (3.103–6.499)	<0.001
Clinical stage						
≤cT2a	327 (50.8)	157 (42.2)	1	0.008	1	0.452
cT2b	170 (26.4)	100 (26.9)	1.225 (0.897–1.673)	0.202	1.133 (0.806–1.593)	0.474
≥cT2c	147 (22.8)	115 (30.9)	1.629 (1.196–2.220)	0.002	1.242 (0.880–1.753)	0.218
MetS (no/yes)						
No	552 (85.7)	286 (76.9)	1	<0.001	1	0.012
Yes	92 (14.3)	86 (23.1)	1.804 (1.301–2.502)		1.583 (1.106–2.266)	
Variable	*Lymph node involvement*					
	Yes, n (%)	*No, n (%)*	*Crude OR (95% CI)*	*P*	*Adjusted OR[a] (95% CI)*	*P*
PSA (ng ml^{-1})						
<10	11 (11.8)	294 (31.9)	1	<0.001	1	<0.001
10≤ PSA <20	15 (16.2)	317 (34.3)	1.265 (0.572–2.798)	0.562	0.882 (0.389–1.997)	0.763
≥20	67 (72.0)	312 (33.8)	5.74 (2.975–11.074)	<0.001	3.478 (1.749–6.916)	<0.001
Biopsy GS						
≤6	0 (0)	330 (35.8)	1	0.094	1	0.064
7	34 (36.6)	317 (34.3)	1.199 (0.917–2.659)	0.141	1.157 (0.876–1.882)	0.177
≥8	59 (63.4)	276 (29.9)	1.740 (0.818–3.003)	0.069	1.541 (0.904–1.910)	0.082
Clinical stage						
≤cT2a	40 (43.0)	444 (48.1)	1	0.041	1	0.417
cT2b	19 (20.4)	251 (27.2)	0.840 (0.476–1.482)	0.548	0.722 (0.396–1.318)	0.288
≥cT2c	34 (36.6)	228 (24.7)	1.655 (1.020–2.686)	0.041	1.088 (0.643–1.842)	0.752
MetS (no/yes)						
No	67 (72.0)	771 (83.5)	1	0.006	1	0.036
Yes	26 (28.0)	152 (16.5)	1.968 (1.212–3.197)		1.751 (1.038–2.955)	

[a]Adjusted for age, smoking status, PSA level, biopsy GS and clinical stage. MetS: metabolic syndrome; PCa: prostate cancer; PSA: prostate-specific antigen; GS: Gleason score; OR: odds ratio; CI: confidence interval

for potential confounders, MetS was associated with an increased risk of prostatectomy GS ≥ 8 (OR = 1.670, 95% CI 1.096–2.545), and with a 1.5-fold increased risk of pT3–4 disease (OR = 1.583, 95% CI 1.106–2.266). Furthermore, the presence of MetS was an independent predictor of lymph node involvement (OR = 1.751, 95% CI 1.038–2.955).

Table 4 indicates crude and adjusted ORs and 95% CIs for pathological features according to the number of MetS components present. A biological gradient was observed between the number of MetS components and the risk of prostatectomy GS ≥ 8, and lymph node involvement, although no statistical significance existed for lymph node involvement. With respect to pathological stage, no obvious biological gradient existed despite marginal significance ($P = 0.060$).

DISCUSSION

Metabolic syndrome is characterized by a cluster of abnormal biochemical factors with a prevalence of 35%–39% among adults in the United States and nearly 20% in China.[16,17] Recent studies have proven a relationship between MetS and increased risk of cancers, including hepatocellular carcinoma, gastric cancer, pancreatic cancer, breast cancer, and colorectal cancer.[18–22] In addition, MetS and its components are likewise associated with tumor progression in some cancers.[23–26]

The relationship between MetS and PCa has also been examined. Although a consensus has not been reached, most researchers have considered MetS and its individual components to be independent risk factors for PCa risk. However, studies focusing on the association between MetS and PCa progression are scarce and inconsistent. A positive association between MetS and higher GS was reported by several research groups,[12,27–29] yet no significant relationship was found between MetS and GS in studies by Beebe-Dimmer *et al*.[30] and Han *et al*.[31] Interestingly, Jeon *et al*.[14] observed that MetS was inversely associated with GS. The present study found that patients with MetS were prone to having a higher GS and lymph node involvement. In addition, a positive association of MetS was observed with ≥ pT3 disease, which is in agreement with the studies conducted by Kheterpal *et al*.[12] However, this positive association was not found in two other studies.[27,30] These discrepancies might be caused by different ethnic backgrounds and MetS definitions. Compared with people in developed countries, the Chinese population has different pharmaceutical interventions and lifestyle modifications. Furthermore, the range of PSA levels was relatively large, and 37.3% of patients had a PSA level over 20 ng ml^{-1} in our setting. Although the association of pathological characteristics with MetS has been adjusted and stratified by PSA levels, potential bias may exist. On the other hand, the criteria adopted by these research groups are not the same. For example, Han *et al*. used National Cholesterol Education Program/Adult Treatment Panel III criterion, which assesses obese status by abdominal circumference;[31] Yet Kheterpal *et al*.[12] employed the criterion defined by the International Diabetes Federation, which is based on BMI ≥ 30 kg m^{-2}. Clearly, further research using large-scale populations is needed.

The relationship between individual component of MetS and worse pathological features of PCa has been reported: patients with higher tumor grade and higher disease stage were more obese and more dyslipidemic, and had elevated visceral adipose tissue accumulation and fasting plasma insulin levels.[32,33] However, MetS is a unification of multiple metabolic components; hence, analyzing MetS as one single variable may be inadequate, and may result in neglecting independent effects and interactions of each individual component. The accumulating impact of MetS components on PCa risk and PCa mortality has also been evaluated. An increasing number of MetS components was correlated with a higher probability of PCa, as well as higher PCa mortality.[32,34] The present study, for the first time, assessed the accumulating effect of each single component of MetS and their association with pathological features. A biological gradient for the relationship of MetS with prostatectomy GS and lymph

Table 4: Association between number of MetS components and pathological features of PCa patients

Number of metabolic components	*Prostatectomy GS*				*Pathological stage*				*Lymph node involvement*			
	≤7, n (%)	*≥8, n (%)*	*Adjusted OR[a] (95% CI)*	*P*	*pT2, n (%)*	*pT3-4, n (%)*	*Adjusted OR[a] (95% CI)*	*P*	*No, n (%)*	*Yes, n (%)*	*Adjusted OR[a] (95% CI)*	*P*
0 components	222 (30.9)	83 (27.9)	1	0.034	200 (31.1)	105 (28.2)	1	0.060	284 (30.8)	21 (22.6)	1	0.338
1 components	253 (35.2)	77 (25.8)	0.792 (0.510-1.230)	0.299	220 (34.2)	110 (29.6)	0.938 (0.653-1.347)	0.729	304 (32.9)	26 (27.9)	1.251 (0.665-2.353)	0.488
2 components	135 (18.8)	73 (24.5)	1.336 (0.833-2.141)	0.229	135 (20.9)	73 (19.6)	0.842 (0.561-1.264)	0.407	184 (19.9)	24 (25.8)	1.627 (0.848-3.122)	0.143
≥3 components	108 (15.1)	65 (21.8)	1.541 (0.937-2.535)	0.089	89 (13.8)	84 (22.6)	1.509 (0.991-2.298)	0.055	151 (16.4)	22 (23.7)	1.730 (0.884-3.383)	0.109

[a]Adjusted for age, smoking status, PSA level, biopsy GS and clinical stage. MetS: metabolic syndrome; PCa: prostate cancer; GS: Gleason score; OR: odds ratio; CI: confidence interval; PSA: prostate-specific antigen

node involvement was observed: as the number of MetS component increased, the risk of GS ≥ 8 and lymph node involvement was elevated, and coexistence was more likely, although there was no significance with lymph node involvement.

The exact method by which MetS influences PCa progression remains uncertain. There are several plausible explanations: based on insulin resistance, MetS denotes dysregulation of the insulin-like growth factor (IGF) signaling pathway, as well as a pro-inflammatory condition and abnormal adipokines levels. IGF-1 has important proliferation stimulation and anti-apoptosis effects on carcinogenesis.[35] It has also been found that IGF-1 can stimulate tumor angiogenesis.[36] Some cytokines associated with a pro-inflammatory state, such as interleukin (IL)-6, IL-8, and cyclooxygenase-2, have all been demonstrated to promote PCa initiation and progression.[37,38] Furthermore, altered levels of circulating adipokines are also associated with PCa risk and PCa invasion.[39,40] Thus, further studies are warranted to reveal the complex molecular mechanisms by which MetS is linked to PCa.

The present study also conveys other clinical implications. Since MetS is considered a possible etiology of PCa, and it might contribute to PCa progression, better control of MetS may prevent PCa development. In addition, accurate preoperative staging is important for the management selection of PCa. Nevertheless, a large portion of tumors are over- or under-staged.[41] Given the association between MetS and pathological features, this information might be helpful to accurately predict stage in MetS patients.

The present study has limitations that merit mentioning. First and foremost, the data were analyzed retrospectively, which carries an intrinsic selection bias. The retrospective design only allowed us to evaluate the temporal association between MetS and PCa progression, thereby causal inferences are limited. Second, some important information, such as family history, diet, and physical activity, and medication usage, including aspirin, anti-diabetes drugs, and statins, was not gathered. These potential confounders might limit the statistical power of this study. In addition, the evaluation of overweight was carried out only by BMI in our study, whereas evidence suggests that waist circumference is more closely related to metabolic changes in comparison with BMI.[42,43] Third, information pertaining to the duration of MetS, which may theoretically influence the natural development of PCa, was also lacking. Finally, all the data were based on Chinese men and thus the results cannot be generalized to other ethnic populations. Further prospective research conducted using large patient groups with a long follow-up is needed.

CONCLUSIONS

In summary, the presence of MetS was associated with an increased risk of higher GS, pT3–4 diseases and lymph node involvement. Furthermore, as the number of MetS components increased, the risk of GS ≥ 8 was elevated, and analogous trends existed for lymph node involvement, despite the lack of statistical significance. Further studies are warranted to assess the possible implication of MetS prevention on PCa development.

AUTHOR CONTRIBUTIONS

GMZ and YZ designed the study, collected, analyzed and interpreted the clinical data, and wrote the manuscript. DHD, CTH and CYG collected part of the patients' clinical data. WJG and XJQ analyzed part of the data. LJS and DWY supervised the project and revised the manuscript. All authors vouch for the respective data and analysis, approved the final version and agreed to publish the manuscript.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

ACKNOWLEDGMENTS

This study was supported in part by grant from the National Natural Science Foundation of China (No. 81272837).

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