RESEARCH ARTICLE

The Metabolic Syndrome is Associated with More Aggressive Prostate Cancer

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Abstract

Purpose: The aim of this study was to analyze any association between the metabolic syndrome (MetS) and risk of prostate cancer (PCa) and cancer grade among men undergoing radical prostatectomy for PCa. Materials and Methods: 50 patients with MetS and 50 patients without MetS who undervent radical prostatectomy (RP) were included in the study. Age at biopsy, height, weight, digital rectal examination (DRE), pre-biopsy PSA levels, prostate volume, histopathologic diagnosis after surgery and gleason scores were collected data from all patients. Histologic material obtained at biopsy was given a Gleason score; tumours with a Gleason score ≥7 were considered high grade and <7 were considered low grade. Results: The mean age at the time of biopsy was 63.7±5.94 in patients with MetS and 61.6±6.14 in patients without MetS. Men with MetS had significantly lower PSA levels (p=0.01) (7.21±2.74 and 8.81±2.72, respectively). Also, the men with MetS had higher RP tumor grade (p=0.04). Conclusions: Men with MetS undergoing RP have lower PSA levels and have significantly higher grade PCa. We must be careful for screening PCa in patients with MetS. Although the patients had lower PSA levels, they may have high grade disease.

Keywords: Metabolic syndrome - prostate cancer - diabetes mellitus - Gleason score - PSA

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Introduction

The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors that includes hypertension, diabetes mellitus, obesity, hypertriglyceridemia, and low high density lipoprotein cholesterol, with insulin resistance as the underlying hallmark feature. The prevalence of MetS has been increasing worldwide and has become a major public health problem in many western countries. For example, 35-41% of adults in the USA are reported to exhibit MetS (Alberti et al., 2009). Recently, increasing evidences suggests that MetS may be involved in the development and progression of certain types of cancer as an independent etiologic factor including breast cancer (Pothiwala et al., 2009), endometrial cancer (Rosato et al., 2011), colorectal cancer (Pelucchi et al., 2010), pancreatic cancer (Rosato et al., 2011), bladder cancer (Ozbek et al., 2014), kidney cancer (Ozbek et al., 2013) and prostate cancer (PCa) (Zhou et al., 2007). Changes in neoplastic metabolism, DNA oxidation damage or repair malfunction, local inflammation, and insulin-like growth factor 1 (IGF-1) may contribute to the relationship between MetS and malignant disease (Renehan et al., 2004; Valko et al., 2004; Guo et al., 2014).

One of these cancers, prostate cancer (PCa) is the most frequently diagnosed malignancy in industrialized countries in men and it is the second most commonly diagnosed cancer and the sixth leading cause of cancer death worldwide (Siegel et al., 2011). Furthermore, several investigators have stated that the aggressiveness of prostate cancer in Asians in North America is more advanced than that of Caucasians and African-Americans at the time of diagnosis. This may depend on geographic, dietary, environmental, and genetic factors (Kang et al., 2013). MetS was firstly observed as a composite factor associated with prostate cancer risk in 2004 (Laukkanen et al., 2011), and more studies have since reported the association between MetS and prostate cancer. A number of studies have found that features of the metabolic syndrome may be predictive of prostate cancer risk. Studies in Scandianvians and in African Americans have found a positive association, while others found an inverse association in a mixed population or no relationship in Scandinavians or Caucasians in the United States of America (Beebe Dimmer et al., 2007; 2009; Martin et al., 2009; Laukkanen et al., 2011). Also, some studies suggest that components of MetS may also result in more aggressive Pca and higher risk (Long et al., 2012). In a previous study, Hammarsten and Hogstedt demonstrated that both PCa stage and grade are directly associated with

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BMI, waist measurement, TG, and fasting plasma insulin, and indirectly with HDL (Hammarsten and Högstedt, 2004).

In present study, we want to analyze the association between MetS with risk of prostate cancer and cancer grade among men undergoing radical prostatectmy for PCa. We compared PSA levels, Gleason score levels, stage and prostate volume between the patients with and without MetS who underwent radical prostatectomy.

Materials and Methods

After obtaining Institutional Review Board approval, we retrospectively determined our 5 years datas and collected data from 100 consecutive patients who underwent radical prostatectomy (RP) at our hospital. 50 patients with MetS and 50 patients without MetS were included in the study.

Assays for serum total and high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and glucose levels were performed in the hospital's chemistry laboratory. MetS was defined according to the guidelines set forth by several organizations: the Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity (2). We took the presence of any three of the following five risk factors as sufficient for diagnosing MetS: (i) elevated waist circumference >88 cm; (ii) elevated TG (>150 mg/dL) or drug treatment for elevated TG; (iii) reduced HDL-C (<50 mg/dL) or drug treatment for reduced HDL-C; (iv) elevated blood pressure (systolic >130 and/or diastolic >85 mm Hg) or antihypertensive drug treatment in a patient with a history of hypertension; and (v) elevated fasting glucose (>100 mg/dL) or drug treatment for elevated glucose.

Age at biopsy, height, weight, digital rectal examination (DRE), pre-biopsy PSA levels, prostate volume, histopathologic diagnosis after surgery and gleason scores were collected data from all patients. Body mass index (BMI) was calculated as weight (Kg) divided by height squared (meters). Patients underwent transrectal ultrasound- guided systematic extended biopsies (12-14 cores) for the evaluation when the PSA level was >2.5 ng/mL or digital rectal examination (DRE) was abnormal. Prostate volume was determined by transrectal ultrasound at time of randomization. After the diagnosis of prostate adenocarcinoma, all patients underwent RP. The pathologic gleason score was assigned according to the 2005 International Society of Urological Pathology consensus (Epstein et al., 2005). Histologic material obtained at biopsy was given a Gleason score; tumours with a Gleason score ≥7 were considered high grade and <7 were considered low grade (Oliver et al., 2004).

Statistical analysis

The baseline characteristics of the controls and the subjects with MetS were compared using a two sample t-test or Mann–Whitney U-test for the continuous variables and a chi-square test or Fisher's exact test for the categorical variables. All statistical tests were two-tailed, and statistical significance was defined as $p<0.05$. All analysis were conducted using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA).

Table 1. Values of Men With and Without MetS who Underwent RP

		Men with MetS	Men without MetS	p value
No of patients		50	50	
Age (mean±sd)		63.74±5.94	61.58±6.14	0.075
BMI (mean±sd)		28.93±2.89	27.35±2.93	0.011*
Preop PSA (mean±sd)		7.21±2.74	8.81±2.72	0.001*
PV (mean±sd)		48.2±14.34	53.28±16.9	0.316
RP gleason score	≥7	21.0 (42%)	9.0 (18%)	0.004*
(n, %)	<7	29.0 (58%)	41.0 (82%)	

*Significant statistical difference between values; MetS: metabolic syndrome; RP: radical prostatectomy; BMI: body mass index; PSA: prostate spesific antigen; PV: prostate volume

Results

The mean age at the time of biopsy was 63.74 in patients with MetS and 61.58 in patients without MetS. There were no statistical difference between groups. Body mass indexes (BMI) were higher in men with MetS than men without MetS (p=0.11). Mean values of BMI was shown in Table 1. Men with MetS had significantly lower PSA levels (p=0.01). Mean PSA level 7.21±2.74 in patients with MetS and 8.81±2.72 in patients without MetS, respectively. Also, the men who have MetS, had higher RP tumor grade than men without MetS (p=0.04). 21 men had gleason score≥7 (42%) in MetS group and 9 men had gleason score≥7 (18%) in nonMetS group.

We found no correlation between MetS and prostate volume in patients who underwent RP (p=0.316). Mean prostate volume was 48.2 ±14.34 in patients with MetS and 53.28±16.9 in patients without MetS. All values of patients with and without MetS were shown in Table 1.

We also evaluated the association between five components of MetS and tumor grade. Just, DM and waist circumference were significantly associated with the high tumor grade (p<0.05). There were no correlation between other three components and tumor grade.

Discussion

Metabolic syndrome was initially described as a cluster of clinical conditions that serve as risk factors for cardiovascular disease with insulin resistance its central component (Beebe Dimmer et al., 2007). However, several studies have demonstrated an association between metabolic syndrome and various cancers (Pothiwala et al., 2009). In this study, we retrospectively reviewed the patients undergoing RP at our institution between March 2007 and October 2011, comparing those with metabolic syndrome to those with no components of the syndrome to assess its potential association on PCa aggressineves.

The classic metabolic syndrome is characterized by visceral obesity, insulin resistance, low HDL-cholesterol, high triglycerides, elevated C-reactive protein, and low adiponectin levels. Insulin resistance and hyperinsulinemia

are the cornerstone of metabolic syndrome and are also factors for prostate cancer. Among the physio-pathological entities that comprise metabolic syndrome, the serum level IGF-I seems to be the one that is most closely linked with prostate cancer. Insulin resistance, which is a fundamental component of MS, plays an important role in malignant formation regarding the intracellular insulin receptor or intrinsic hormone metabolism. In particular, insulin and IGF-1 facilitate cell proliferation and suppress apoptosis (Khandwala et al., 2000). Animal studies have also revealed that removal of IGF-1 receptor or lowering of the IGF-1 level decreases malignant for- mation (LeRoith and Roberts, 2003). An epidemiologic investigation also linked increasing IGF-1 level to prostate cancer (Chan et al., 1998) and supported the suggestion that overactivity of male hormone levels in- duced by insulin resistance, increased IGF-1 level, and de- creased IGF binding protein level would also be related to prostate cancer. Also, in a previous study, hyperinsulinemia-the cornerstone of metabolic syndrome, appear to be associated with a higher risk of prostate cancer (Pandeya et al., 2014). Other associations of metabolic syndrome and CaP risk have been suggested. Leptin, a cytokine produced by white adipose tissue, influences cellular differentiation and CaP. However, studies of leptin levels and CaP aggressiveness have been inconclusive (Buschemeyer and Freedland, 2007; Hsing et al., 2007). Obesity is also associated with decreased serum adiponectin, also produced by adipocytes, and has been suggested to have anti-angiogenic properties .

Because of this strong association between MetS and PCa, we compared the PCa aggressiveness in men with or without MetS. We found that the men who have MetS, had higher RP tumor grade than men without MetS (p=0.04). 21 men had gleason score ≥7 (42%) in MetS group and 9 men had gleason score ≥7 (18%) in nonMetS group. In a previous study, De Nunzio et al. (2011) have suggested that MetS could be associated with more aggressive tumours based on their analysis. They found a greater risk of high grade tumours, defined by a Gleason score ≥7. Unfortunately they could not associate MS with Gleason score 8-10 because of the limited number of patients. Our results support the hypothesis that MS is associated with a significant increase of high grade tumours. Like our study, some studies suggest that components of MetS may also result in more aggressive PCa. Hammarsten and Högstedt (2004) demonstrated that both PCa stage and grade are directly associated with BMI, waist measurement, TG, and fasting plasma insulin, and indirectly with HDL. The cause of this association between MetS and PCa, may be low testosterone. Low testosterone, a condition associated with MetS, has also been linked to more severe PCa. In retrospective analysis, men with low total plasma testosterone (<3 ng/mL) had an elevated risk of high-grade PCa (Gleason score ≥7; OR, 2.59) (Platz et al., 2005). Low testosterone levels have also been significantly related to more advanced PCa stages and positive margins in radical retropubic prostatectomy (Teloken et al., 2005). Otherwise, in a previous study the authors reported that the presence of MetS was associated with a significantly decreased risk of high-grade prostate cancer (OR, 0.101; 95% CI, 0.022 to 0.473; p=0.004) (Kyoung et al., 2012).

In our study, we also evaluated the preoperative PSA levels of men with and without MetS. As we know, the prostate specific antigen (PSA) test is used worldwide as a screening tool, as part of the diagnostic workup to rule out prostate cancer, and in the management of this disease after diagnosis. Several studies have examined the association between various metabolic risk factors and PSA level (Werny et al., 2006; Parekh et al., 2008). A study by Kim et al. in investigating the association of metabolic syndrome and serum PSA level in a group of 2,007 men (aged 30 to 79 years) without prostate cancer, found that the prevalence and sum of metabolic syndrome components were inversely associated with serum PSA levels. Multivariate analysis showed that serum PSA levels were strongly associated with abdominal obesity and impaired fasting glucose levels (Kim et al., 2008). Studies have reported that obesity was associated with decreased PSA levels and an enlarged prostate volume may decrease the sensitivity of prostate biopsy, perhaps leading to delay in the detection of prostate cancer (Kristal et al., 2006). As previous studies, we found lower PSA levels in PCa patients with MetS. Because of that men with MetS are less likely to undergo prostate biopsy and thus are less likely to be diagnosed with PCa. This delay on diagnosis may cause that the men had high grade PCa at the diagnosis. Other explanation, although patients with metabolic syndrome may have an artificially low PSA values (relative to the control group) due to decreased serum testosterone levels and the dilutional effect of greater plasma volume in obese patients, it cannot completely explain the significant increased Gleason grade and tumor stage on final pathology.

The present study is limited by the retrospective nature of our cohort. Our population represents patients at high risk for prostate cancer (elevated PSA and/or abnormal DRE) and thus may not be generalizable to all men at risk of prostate cancer. Moreover, we did not assess information on physical activity or diet, which are associated with MetS, risk of prostate cancer, and potentially cancer grade at diagnosis.

In conclusion, men with MetS who underwent RP, have lower PSA levels and have significantly higher grade PCa. We must be careful for screening PCa in patients with MetS. Although the patients had lower PSA levels, they would have high grade disease. Further prospective studies in larger patient groups with long-term follow-up as well as basic research are needed to clarify the relationship between the components of MS and prostate cancer and to evaluate the possible implication of MS prevention on prostate cancer development.

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