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Dissecting the Association Between Metabolic Syndrome and Prostate Cancer Risk: Analysis of a Large Clinical Cohort

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Abstract

Background: A biologic rationale exists for the association between metabolic syndrome (MetS) and prostate cancer (PCa). However, epidemiologic studies have been conflicting.
Objective: To evaluate the association between MetS and the odds of PCa diagnosis in men referred for biopsy.
Design, setting, and participants: Patients without prior PCa diagnosis undergoing prostate biopsy were identified from a large prostate biopsy cohort (in Toronto, Canada). The definition of MetS was based on the most recent interim joint consensus definition, requiring any three of five components (obesity, elevated blood pressure, diabetes or impaired fasting glucose, low high-density lipoprotein-cholesterol, and hypertriglyceridemia). Both the individual components of MetS and the cumulative number of MetS components were evaluated.
Outcome measurements and statistical analysis: The outcomes were PCa detection overall, clinically significant PCa (CSPC; defined as any Gleason pattern $\geq$4, >50% involvement of a single biopsy core, or more than one of three total number of cores involved), and intermediate- or high-grade PCa (I-HGPC; Gleason 7–10). Tests for trend and multivariable logistic regression analyses were performed.
Results and limitations: Of 2235 patients, 494 (22.1%) had MetS. No individual MetS component was independently associated with PCa. However, increasing number of MetS components was associated with higher PCa grade ($p < 0.001$), as well as progressively higher odds of PCa outcomes (three or more; ie, MetS) compared with no MetS components: Odds ratios were 1.54 for PCa overall (95% confidence interval [CI], 1.17–2.04; $p = 0.002$), 1.56 for CSPC (95% CI, 1.17–2.08; $p = 0.002$), and 1.56 for I-HGPC (95% CI, 1.16–2.10; $p = 0.003$) in multivariable analyses. The main limitation is the retrospective design.
Conclusions: Although the individual MetS components are not independently associated with PCa outcomes, MetS is significantly associated with higher odds of PCa diagnosis, CSPC, and I-HGPC. There is a biologic gradient between the number of MetS components and the risk of PCa, as well as cancer grade.
Patient summary: Metabolic syndrome is a collection of metabolic abnormalities that increases one's risk for heart disease. Our study shows that an increasing degree of metabolic abnormality is also associated with an increased risk of diagnosis of overall and aggressive prostate cancer.

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1. Introduction

Metabolic syndrome (MetS) is a constellation of metabolic risk factors that increases an individual's risk of cardiovascular disease and diabetes [1]. It results from dietary caloric excess and a sedentary lifestyle.

Links between MetS and risk of developing prostate cancer (PCa) are emerging. At the biochemical level, several perturbations in cellular signaling systems and derangements in circulating levels of biologic mediators are associated with MetS and have been implicated in cancer risk and progression [2,3]. The epidemiologic evidence, conversely, although generally in favor of an association between MetS and PCa, is somewhat conflicting [4–14].

Thus although there is a strong argument for biologic plausibility, further supporting clinical evidence is needed. Our overall objective was to evaluate the association between MetS and PCa diagnosis in a large clinical cohort undergoing prostate biopsy to perform a detailed examination of PCa grade. Our specific objectives were to determine if MetS and/or its individual components are associated with PCa diagnosis, and to determine if there is a biologic gradient in the association between the number of MetS components and the odds of PCa diagnosis.

2. Methods

2.1. Patients and data collection

Patients without a prior PCa diagnosis undergoing transrectal ultrasound (TRUS)-guided prostate biopsy (2003–2013) were identified using our institutional Genitourinary BioBank [15,16]. Patients were required to have a clinical chart available in our institutional electronic health records for review. Patients on active surveillance at the time of biopsy were excluded. For patients with multiple biopsies, the most recent was used to minimize the inclusion of known false-negative biopsies (ie, when repeat biopsy detected a cancer missed on initial biopsy). Research ethics board approval was obtained, and patient consent was sought for inclusion in the database.

Clinical data were obtained through patient questionnaires (ethnicity, family history of PCa, prior biopsy history, and medication history) and/or electronic chart review (age, past medical and medication history, digital rectal examination findings, blood tests, prostate volume, pathology results). Height and weight were measured at the time of biopsy to compute body mass index (BMI). TRUS and biopsies were performed by a single high-volume radiologist. First-time biopsies generally involved 10–12 cores; repeat biopsies involved 13–18 cores. Additional cores were taken if suspicious lesions were seen on TRUS. Biopsies were read by genitourinary pathologists.

2.2. Primary exposure

The presence of MetS was assessed around the time of biopsy. Our study definition of MetS was modeled after the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and International Diabetes Federation interim consensus statement [1], and requires any three of the five MetS components (Table 1). Our definition differs in two ways from the interim consensus statement. First, BMI was used instead of waist circumference, as was done in another study of MetS and PCa [12]. Controversy exists regarding which anthropometric measure is best for predicting an individual's future risk of diabetes and cardiovascular disease [17]. However, for the purpose of evaluating an overall biologic association, conclusions would likely be similar using either BMI or waist circumference given the strong correlation between the two measures (Pearson correlation: 0.88–0.94 in men) [18]. The second difference is that the interim consensus definition of elevated blood pressure is ≥130/85 mm Hg, or physician diagnosis or medical treatment, whereas our study definition only uses the latter two because blood pressure measurements were not uniformly available. MetS was analyzed dichotomously and as a four-level categorical variable (based on number of components present: 0, 1, 2, or ≥3).

Table 1 – Study criteria for metabolic syndrome

Criteria for metabolic syndrome
Diagnosis of metabolic syndrome requires *any three* of the following:
• Obesity, defined as body mass index ≥30 kg/m^2
• Elevated serum triglycerides, defined as ≥150 mg/dl (1.7 mmol/l) on fasting lipid profile, or treatment for this abnormality
• Reduced serum high-density lipoprotein-cholesterol, defined as <40 mg/dl (1.03 mmol/l) in men on fasting lipid profile, or treatment for this abnormality
• Elevated blood pressure, defined based on physician diagnosis of hypertension or use of antihypertensive medications
• Elevated fasting glucose, defined as ≥100 mg/dl (5.6 mmol/l), or use of medication for hyperglycemia, or physician-diagnosed type 2 diabetes mellitus
Adapted from the American Heart Association/National Heart, Lung, and Blood Institute and International Diabetes Federation interim consensus statement [1].

2.3. Outcome measures

Three PCa biopsy outcomes were studied. The first was overall diagnosis of PCa. The second was diagnosis of clinically significant PCa (CSPC, defined as any Gleason pattern ≥4, >50% of involvement of any single biopsy core, or greater than one of three of the total number of cores involved). The third was diagnosis of intermediate- or high-grade PCa (I-HGPC), defined by a Gleason sum of 7–10.

2.4. Statistical analysis

Statistical analyses were performed using SAS v.9.3 (SAS Institute Inc., Cary, NC, USA). Cohort characteristics were compared between patients with and without MetS. The Cochran-Armitage test for trend (used when comparing a dichotomous and an ordinal categorical variable) and the Mantel-Haenszel chi-square test (tests the linear association between two ordinal categorical variables) were used to evaluate the association between MetS and PCa grade.

To assess the independent effect of each component, multivariable logistic regression models were constructed by including all five MetS components along with a priori identified potential confounders: age, ethnicity, family history of PCa, prostate volume, history of prior prostate biopsy, and use of 5α-reductase inhibitors at the time of biopsy. Prostate volume was log-transformed because it was non-normally distributed.

The associations between number of MetS components and PCa outcomes were first examined with the Cochran-Armitage test. The independent associations between MetS, the number of its components, and PCa outcomes were then examined using a multivariable logistic regression model adjusting for the covariates previously listed. Statistical model assumptions were verified.

Given literature reporting an association between obesity and PCa [19], we sought to evaluate whether obesity is the primary driver of the association between MetS and PCa diagnosis by adding obesity to the multivariable model with MetS. We also sought to determine if the association between MetS and PCa diagnosis is different among obese