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Original article

Metabolic syndrome and low high-density lipoprotein cholesterol are associated with adverse pathological features in patients with prostate cancer treated by radical prostatectomy

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Abstract

Background: Previous studies have suggested a link between metabolic syndrome (MetS) and prostate cancer (PCa). In the present study, we aimed to assess the association between MetS and markers of PCa aggressiveness on radical prostatectomy (RP).

Methods: All patients consecutively treated for PCa by RP in 6 academic institutions between August 2013 and July 2016 were included. MetS was defined as at least 3 of 5 components (obesity, elevated blood pressure, diabetes, low high-density lipoprotein (HDL)-cholesterol, and hypertriglyceridemia). Demographic, biological, and clinical parameters were prospectively collected, including: age, biopsy results, preoperative serum prostate-specific antigen, surgical procedure, and pathological data of RP specimen. Locally advanced disease was defined as a pT-stage ≥3. International Society of Urological Pathology (ISUP) groups were used for pathological grading. Qualitative and quantitative variables were compared using chi-square and Wilcoxon tests; logistic regression analyses assessed the association of MetS and its components with pathological data. Statistical significance was defined as a $P < 0.05$.

Results: Among 567 men, 249 (44%) had MetS. In a multivariate model including preoperative prostate-specific antigen, biopsy ISUP-score, clinical T-stage, age, and ethnicity: we found that MetS was an independent risk factor for positive margins, and ISUP group ≥4 on the RP specimen (odds ratio [OR] = 1.5; 95% CI: 1.1–2.3; $P = 0.035$; OR = 2.0; 95% CI: 1.1–4.0; $P = 0.044$, respectively). In addition, low HDL-cholesterol level was associated with locally advanced PCa (OR = 1.6; 95% CI: 1.1–2.4; $P = 0.024$). Risks of adverse pathological features increased with the number of MetS components: having ≥ 4 MetS components was significantly associated with higher

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risk of ISUP group ≥ 4 and higher risk of positive margins (OR = 1.9; 95% CI: 1.1–3.3; $P = 0.017$; OR = 1.8; 95% CI: 1.1–2.8; $P = 0.007$, respectively).

Conclusion: MetS was an independent predictive factor for higher ISUP group and positive margins at RP. Low HDL-cholesterol alone, and having 4 and more MetS components were also associated with higher risk of adverse pathological features.

Keywords: Prostatectomy; Prostatic neoplasm; Metabolic syndrome; Prognosis; Cholesterol; HDL

1. Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer worldwide [1]. There is growing evidence that diet and obesity might influence the prognosis of several malignancies, including PCa [2–10]. Metabolic syndrome (MetS) results from dietary excess and sedentary lifestyle in genetically susceptible patients. MetS comprises a combination of at least 3 of the following conditions: obesity, elevated fasting glucose, elevated triglycerides, reduced high-density lipoprotein (HDL), and high blood pressure (National Cholesterol Education Program–Adult Treatment Panel III definition) [11]. Previous studies have suggested that MetS might be associated with markers of PCa aggressiveness, and might influence disease prognosis, even though some of these studies provide conflicting results [2–10,12–15].

Most of the published studies focused on the role of MetS at the time of PCa diagnosis, therefore based on biopsy data [4–6,12,13]. Studies from biopsy results are subject to sampling error, since biopsy analysis may underestimate PCa pathological characteristics [2,3,15,16]. On the other side, analysis of the radical prostatectomy (RP) specimen allows for a reliable assessment of PCa grade and stage [2,3]. Our hypothesis is that MetS status and its components might influence PCa prognosis. Thus, we aimed to determine if MetS could predict adverse pathological features on RP specimen, in a multicentric prospective study.

2. Patients and methods

This prospective multicentric study was conducted according to Good Clinical Practice regulations and the Declaration of Helsinki. The local Ethics Committee approved the protocol. All patients gave their written informed consent to participate before any study-related activities were performed.

All patients who underwent RP for PCa at 6 French academic institutions between August 2013 and July 2016 were prospectively included in the study ($n = 757$). Demographic, biological, and clinical parameters were prospectively collected, including: age, ethnicity, PCa family history, prostate biopsy results, prostate magnetic resonance imaging results, preop serum prostate-specific antigen (PSA, ng/ml), cholesterol (mmol/l), triglycerides (mmol/l), HDL-cholesterol (HDL-C) (mmol/l), fasting glucose (mmol/l), abdominal perimeter (cm), blood pressure (mmHg). All these criteria were collected prospectively at inclusion and before surgery. Surgical outcomes were also prospectively collected: surgical approach, nerve sparing, and pathological characteristics of the RP specimen.

The definition of MetS was defined as the presence of at least 3 of the following criteria: abdominal perimeter ≥102 cm (or 40 inches), elevated serum triglycerides (≥1.7 mmol/l or ≥150 mg/dl, or dyslipidemia treatment), reduced serum HDL-C (<1.03 mmol/l or <40 mg/dl), elevated blood pressure (≥130/85 mmHg or use of anti-hypertensive medications), and elevated fasting glucose (fasting glucose ≥5.6 mmol/l or ≥100 mg/dl or use of medications for hyperglycemia) (National Cholesterol Education Program–Adult Treatment Panel III definition) [11]. Locally advanced disease was defined as a pT-stage ≥3. International Society of Urological Pathology (ISUP) groups were used for pathological grading [17]. Specimen analysis was performed in each center. Patients without complete pathological reports ($n = 21$), and patients with missing data to determine the MetS status ($n = 149$) were excluded from the study. A total of 567 men were included in the analysis.

Qualitative and quantitative variables were compared using chi-square and Wilcoxon tests; Logistic regression analyses assessed the association of Mets and its components with pathological data, all parameters assessed in univariable analysis were included in multivariable analysis in order to avoid unforeseen confounding bias owing to complex interrelationship among the variables. All P values were 2-sided, and statistical significance was defined as a $P < 0.05$. Statistical analyses were performed using SPSS15.0 Software (IBM Corp., Armonk, NY).

3. Results

Among the 567 men included in the study, 249 (44%) had a MetS. Median age was 64 (45–79) years. Median body mass index was 26.0 (16.0–40.0) kg/cm^2. When compared to patients without MetS, patients with MetS showed significantly higher body mass index, higher abdominal perimeter, higher total cholesterol, higher triglycerides, higher blood pressure, higher glycemia, and lower HDL-C (<0.001). Dyslipidemia treatment was taken by 119/249 (48%) of patients with MetS vs. 26/318 (8%) of patients without MetS (<0.001). There were no significant