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Patients with metabolic syndrome and widespread high grade prostatic intraepithelial neoplasia are at a higher risk factor of prostate cancer on re-biopsy: A prospective single cohort study

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Abstract

Objectives: To test the hypothesis that patients with widespread high grade prostatic intra epithelial neoplasia (wHGPIN) and metabolic syndrome (MetS) are at a higher risk of prostate cancer (PCa) at a repeat biopsy.

Methods and Materials: We prospectively evaluated 161 patients submitted from December 2004 to December 2011 to prostate rebiopsy after a initial diagnosis of HGPIN in a tertiary academic center. A 12 core biopsy template was used for all the biopsies. Rebiopsy was performed six months after the initial biopsy independently from PSA level and the DRE finding. wHGPIN was defined as ≥ 4 biopsy cores involved. MetS was defined according to the National Cholesterol Education Program's Adult Treatment Panel III criteria.

Results: Overall, 64 patients (39.7%) presented wHGPIN and 97 isolated HGPIN (60.3%). MetS was found in 63 patients, 39.1% of the whole population. Out of them 16 (25.3%) and 47 (74.7%) patients had a diagnosis of isolated and wHGPIN ($P = 0.001$). PCa detection rate at repeat biopsy was significantly higher in patients with MetS and wHGPIN than in those with wHGPIN and no MetS (57.4% Vs 23.5%; $P = 0.016$). A logistic regression model confirmed that wHGPIN and MetS are independent risk factors of prostate cancer diagnosis (respectively: Odds ratio (OR) = 4.187, 95%CI: 1.65–10.57 $p = 0.002$ and OR = 3.603, 95%CI: 1.41-9.19, $p = 0.007$).

Conclusion: Patients with MetS and wHGPIN are at a higher risk of PCa, therefore performing a new prostate biopsy in those patients should be recommended.

Keywords: metabolic syndrome (MetS); high grade prostatic intraepithelial neoplasia (HGPIN); chronic prostate inflammation; prostate cancer (PCa).

1. Introduction

Prostatic intraepithelial neoplasia (PIN) can be described as a neoplastic transformation of the secretory epithelium lining, prostatic ducts and acini with the process confined to the epithelium [1]. In its original description, PIN was divided into three grades but for the low reproducibility among pathologists these categories were subsequently ranked into low- and high- grade (HGPIN).

HGPIN is also considered a precursor of prostatic cancer in the era of extended biopsy. However, the risk of prostate cancer on subsequent biopsy, approximately 22%, is similar to finding cancer after an initial benign diagnosis [2,3]. Furthermore, in patients with HGPIN, prostate specific antigen (PSA) and digital rectal examination (DRE) are not able to identify which patients are at a higher risk of PCa on subsequent biopsy [4].

Recently, the number of biopsy cores involved in HGPIN is considered one of the pathological findings which predicts a high risk of prostate cancer on successive biopsy [2,5]. Therefore, several studies [3,6,7] and the EAU Guidelines 2012 [5] suggested performing a new biopsy, especially in the case of widespread HGPIN diagnosis. However, no general consensus exists on when prostate biopsy has to be repeated.

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Identifying further clinical and biological high risk predictive factors may reduce the number of needless prostate rebiopsies, while helping to define the rebiopsy time and understand the cancer pathogenesis.

Recently, there is enthusiastic interest in the relationship between Metabolic Syndrome (MetS) and PCa connected to some clinical and epidemiological studies that indicate the metabolic syndrome as a feasible pathogenic cause for prostate cancer [8].

MetS is a complex disorder defined by a cluster of interconnected disorders that increase the risk of cardiovascular disease and diabetes [9]. Moreover, MetS is conceived as a pro inflammatory disease [10] and this status may have a possible role in cancer carcinogenesis [11].

Chronic inflammation of the prostate has been reported as a potential environmental factor in PCa development through the promotion of proliferative inflammatory atrophy (PIA) and HGPIN [11].

Up to now, neither the possible relationship between MetS and HGPIN nor the possible role of MetS as a possible risk factor for PCa in patients with HGPIN has been investigated.

The aim of our study was to test the hypothesis that patients with widespread HGPIN and MetS are at a higher risk of PCa on a re-biopsy .

2. Materials and Methods

From December 2004 to December 2011, patients with a previous diagnosis of HGPIN were listed for a new prostate biopsy six months after the initial diagnosis regardless of the PSA value or DRE finding. Signed informed consent and local ethical committee approval (n° RS80/11) were obtained. Patients on finasteride or dutasteride therapy and patients who had undergone previous prostate surgery were excluded from the series.

Before the biopsy procedure, patients underwent a detailed physical examination to evaluate DRE, height, weight and waist circumference. Blood pressure was also recorded. Fasting (8 h) blood samples were collected to analyze blood glucose, HDL cholesterol, triglycerides and total and free PSA.

All prostate biopsies were carried out as an outpatient procedure, using a 12 core TRUS guided template and a periprostatic anaesthetic block [12]. An antibiotic prophylaxis (Levofloxacin 250 mg b.i.d.), was started 48 h before the biopsy and continued for 72 h after the procedure, and a fleet enema 1–2 h before the biopsy was administrated. One single pathologist who was blinded for the clinical data, except age, was involved in the study.

Metabolic Syndrome (MetS) was defined according to the National Cholesterol Education Program's Adult Treatment Panel III (ATPIII) [8,13]. Patients with at least 3 of the following factors were considered to have MetS: abdominal obesity (waist circumference >102 cm), hypertriglyceridemia (≥ 150 mg/dl), low high density lipoprotein (HDL) cholesterol (<40 mg/dl in men), high blood pressure ($\geq 130/85$ mmHg) and a high fasting blood glucose level (≥ 110 mg/dl).

Widespread HGPIN was defined as four or more cores involved in prostate biopsy, as previously described by Epstein et al. [3].

2.1. Statistical analysis

The Shapiro–Wilk test demonstrated a non normal distribution of the study data set. Consequently, the Mann Whitney for continuous variables and Chi Square test for categorical variables were used to estimate statistical significance. Data are presented as median and interquartile range (IQR: 25th to 75th percentile).

The data were used to define a bivariate logistic regression model in which the presence or absence of prostate cancer on repeat biopsy was analyzed in relation to investigated clinical and pathological variables (age, prostate volume, total and ratio PSA, MetS presence or absence, widespread HGPIN presence or absence). An alpha value of 0.05 was adopted for the level of significance. The Statistical Package for Social Sciences (SPSS) 18.0 for Windows was used to perform the statistical analysis.

3. Results

Overall, one hundred and sixty one patients were enrolled. The median age was 67 (IQR 62–72). Out of them, 97 patients with an initial diagnosis of isolated HGPIN and 64 patients with widespread HGPIN had a repeat biopsy.

Table 1 illustrates the overall clinical characteristics of the study population. No significant differences between patients with isolated and widespread HGPIN were observed for age, prostate volume, total and ratio PSA.

Regarding the MetS status, 63 patients (39.1% of the whole sample) presented MetS according to the ATPIII system. Out of them, 16 patients (25.3%) and 47 (74.7%) patients had a diagnosis of isolated and widespread HGPIN respectively ($p = 0.001$) at initial biopsy (Table 1).

Prostate cancer detection on second biopsy was significantly associated with the presence of widespread HGPIN on a previous biopsy (Table 2). Prostate cancer was observed in 42 patients: 11 (11.5%) in isolated HGPIN and 31 (48.4%) in widespread HGPIN ($p = 0.001$).

Finally, prostate cancer was diagnosed more frequently in patients with MetS and previous widespread HGPIN diagnosis than in patients with widespread HGPIN and normal metabolic status: 57.4% Vs 23.5% ($p = 0.016$) (Table 3).

As a result of multivariate logistic regression analysis, widespread HGPIN and MetS were the only independent variables which increased the risk of prostate cancer on repeat biopsy: respectively OR = 4.187, 95%