Fat boosts, while androgen receptor activation counteracts, BPH-associated prostate inflammation

Linda Vignozzi1, Mauro Gacci2, Ilaria Cellai2, Raffaella Santi1, Giovanni Corona1, AnnaMaria Morelli1, Giulia Rastrelli2, Paolo Comoglio2, Arcangelo Sebastianelli2, Elena Maneschi1, Gabriella Nesti1, Cinzio Del Nunzi2, Andrea Tobar2, Eduardo Mannuccio3, Marco Carinci2, Mario Maggi MD.

1. Sexual Medicine and Andrology Unit, Department of Experimental and Clinical Biomedicine, University of Florence, 2 Department of Urology, 3 Department of Critical Care Medicine and Surgery, Division of Pathological Anatomy, University of Florence
2. Endocrinology Unit, Medical Department, Azienda UL, Maggiore-Bellaria Hospital, Bologna, Italy
3. Department of Urology, Ospedale di Careggi, Università di Firenze, Firenze, Italy
4. Diabetic Section Geriatric Unit, Department of Critical Care, University of Florence, Italy

Table 1

<table>
<thead>
<tr>
<th>DIABETES SCORE (IS)</th>
<th>p for trend</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. IL6 (pg/10^4 cells)</td>
<td>0.059</td>
<td>21.6</td>
<td>25.1</td>
<td>28.6</td>
<td>31.3</td>
<td>33.8</td>
<td>36.4</td>
</tr>
<tr>
<td>b. IL8 (pg/10^4 cells)</td>
<td>0.059</td>
<td>21.6</td>
<td>25.1</td>
<td>28.6</td>
<td>31.3</td>
<td>33.8</td>
<td>36.4</td>
</tr>
<tr>
<td>c. LOX-1 mRNA/18S (% of control)</td>
<td>0.059</td>
<td>21.6</td>
<td>25.1</td>
<td>28.6</td>
<td>31.3</td>
<td>33.8</td>
<td>36.4</td>
</tr>
</tbody>
</table>

Background

The condition known as benign prostatic hyperplasia (BPH) is the most frequent benign neoplasm in men. Although primarily characterized by increased prevalence of both myofibroblast and epithelial cells, more recent epidemiological and histopathological studies have suggested that chronic inflammation in the gland even in BPH pathogenesis.

The nature of this immune dysregulation is almost completely unknown. Epidemiological studies have also demonstrated that BPH is a common clinical finding in male patients affected by metabolic syndrome (MetS), suggesting that a metabolic insult could contribute to the pathogenesis and progression of BPH.

AIM:

1. To investigate whether MetS is associated with BPH-related inflammation in BPH patients undergoing prostatectomy for BPH

2. To investigate the in vitro inflammatory effects of different metabolic insults on human prostatic myofibroblast cells isolated from BPH patients (hBPH).

We have therefore examined the histological characteristics of inflammatory infiltrates (Inflammatory score, IS) in prostatic tissue specimens from a cohort of BPH patients and their correlation with pre-operative MetS features, including hyperglycaemia.

A series of in vitro experiments stimulating myofibroblast hBPH cells with different metabolic stimuli was also performed.

Study Population

Between January 2020 and September 2021, 244 consecutive patients undergoing prostate surgery for BPH were selected for this study in two tertiary referral centres for LUTS/BPH. Ethical permission for this study was obtained from the Azienda Ospedaliero-Universitaria di Firenze (cohort Ethical Committee Ethics Committee of the Azienda Ospedaliero-Universitaria di Firenze), with standard informed consent from the patients for use of their anonymous data. The inclusion criteria were: prostate surgery for severe LUTS due to BPH not responding to conventional medical treatment (i.e., beta-3-reductase inhibitors); ability to communicate, understand and comply with study requirements, and written informed consent. Exclusion criteria were: history of previous prostate surgery, chronic reddish neoplasm and/or urinary infection or bladder stone, known inflammatory disease including prostate cancer, and chronic renal failure. Men with chronic use of anti-inflammatory medications were excluded from the study, while apocrine use of these drugs was allowed. The main characteristics of the samples are summarized in Table 1.

The inflammatory score (IS) significantly increased as a function of MetS components. Among MetS components, in particular, increased HDL cholesterol and elevated triglycerides but not high waist circumference, glycemic, or blood pressure were significantly associated with elevated IS.

CLINICAL STUDY

In the cohort of patients in whom hFVIIa evaluation was available (n=120), the prevalence of hyperglycaemia (77.5%) was detected in 24% of subjects. In this population, hFVIIa was significantly associated with hyperglycaemia (β = 0.920, p=0.001). Furthermore, among the modified MetS parameters, hyperglycaemia, age, and HDL cholesterol were still significantly associated with hFVIIa (β = 0.431, p=0.007). Among the other parameters, triglycerides and IL8 were also significantly increased. Conversely, no significant modification of the TNFα (β = 0.431, p=0.007) and IL-6 type IS was observed, although TNFα was significantly reduced in the MetS group. These findings indicate that MetS also significantly increased inflammation in BPH patients undergoing prostatectomy. Furthermore, in keeping with the overall pro-inflammatory effects of IL8 on myofibroblast hBPH cells, secretion of the anti-inflammatory cytokines IL-10 and IL-18 were significantly inhibited.

CONCLUSIONS

We demonstrated that MetS, and in particular dyslipidaemia, is associated with prostate inflammation. Fats could have, therefore, a detrimental effect on prostate cells, boosting prostate inflammation, a key factor in the development and progression of BPH/LUTS. DHT activity in culturing lipid- and insulin–induced proliferative effects, suggesting that testosterone – via its conversion into DHT – might have unexpected beneficial effects on prostate health. Clinical studies specifically addressing this point are urgently needed.