PROSTATIC INFLAMMATION IS DETERMINANT FOR PROSTATE OVERGROWTH AND LUTS SEVERITY IN MEN WITH METABOLIC SYNDROME: HIGHLIGHTS FROM TWO RECENTLY PUBLISHED MULTICENTRE STUDIES

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ABSTRACT

Introduction: Several evidences have pointed out the possible association between Metabolic Syndrome (MetS) and low urinary tract symptoms (LUTS)/benign prostate hyperplasia (BPH). Recent epidemiological and histopatological evidences suggested chronic inflammation is a crucial event in BPH pathogenesis. Aim of this study is to demonstrate the correlation among pre-operatory LUTS/BPH severity, MetS features and inflammatory infiltrates in prostatectomy specimens of patients with BPH, highlighting the results of two recently published multicentre studies analyzing all the data from a preclinical and clinical point of view.

Materials and methods: We conducted two retrospective study in 271 and 244 consecutive men treated with simple prostatectomy for LUTS/BPH in two tertiary referral centres. Prostate diameters and volume were measured by transrectal ultrasound, LUTS were scored by IPSS, and obstruction diagnosed by uroflowmetry. MetS was defined according to DF & AHA/NHLBI criteria. The inflammatory infiltrate was investigated according to the scoring system of chronic prostatitis (CP-CPPS) and scored as inflammation score (IS) ranging 3 to 9 and glandular disruption (GD). In addition, we investigated the in vitro inflammatory effects of metabolic insults on human prostatic myofibroblast cells isolated from BPH patients (hBPH).

Results: Of 271 men, 86 (31.7%) were affected by MetS. Prostatic volume and the anterior-posterior (AP) diameter were positively associated to the number of MetS components. Among MetS determinants, only dyslipidaemia (increased serum triglycerides and reduced serum HDL levels) was significantly associated with an increased risk of having a prostatic volume >60cm3. IS in prostatectomy specimens showed a step-wise association with number of MetS factors (p=0.001). Dyslipidaemia was the only factor significantly associated with IS. Positive significant correlations among MetS, IS, GD and IPSS Scores were observed. In myofibroblastic hBPH oxidized low-density lipoprotein (oxLDL) showed the highest secretion of IL-8 (>10-folds)-a surrogate marker of prostate inflammation-as well as IL-6, and bFGF.

Conclusions: MetS and dyslipidaemia are associated with prostate overgrowth and inflammation. In particular, with a selective increase of prostatic AP diameter, leading to a modification of prostatic shape. Hence, MetS can be regarded as a new determinant of prostate inflammation and BPH progression in men with severe LUTS.

Keywords: bladder cancer, follow-up, neobladder, radical cystectomy.

INTRODUCTION

Benign prostatic hyperplasia (BPH), considered as a chronic disease with early initiation, slow progression and high prevalence in the adult male, is frequently associated with lower urinary tract symptoms (LUTS) in elderly men.[1] Traditionally, male LUTS were thought to be merely caused by a benign prostatic enlargement (BPE). However, the lack of a complete correspondence between BPE and LUTS has meant a struggle to identify other causative relationships linking prostatic overgrowth, bladder outlet obstruction and LUTS.[2]

Emerging data indicate that a spectrum of age-related disorders, such as metabolic syndrome (MetS), type 2 diabetes (T2DM), cardiovascular (CV) disease, hypogonadism or a combination thereof, have a heretofore unrecognised negative impact on LUTS. Several MetS components have been closely associated with BPH, suggesting that MetS has very heterogeneous clinical ramification.[3-5]

The faster development and progression of symptomatic BPH[3] and a consequent major request of BPH surgery[6] in men with metabolic alterations, supports the hypothesis that pathological alterations characterising MetS can also influence the prostatic overgrowth and the development of LUTS. Although the molecular and cellular mechanisms involved in stromal and epithelial prostate modification leading to BPH/LUTS remain unclear, chronic inflammation has been proposed as a candidate promoter mechanism, and MetS can broadly be considered a systemic inflammatory state and a chronic inflammation-driven tissue remodelling and overgrowth.[7] Preclinical studies in genomic and non-genomic animal models of different metabolic diseases have suggested a potential causative association between metabolic derangements and BPH development and progression.[8]

The aim of this paper is to examine the correlation among pre-operatory LUTS/BPH severity and MetS features, to evaluate whether MetS is associated with BPH-related inflammation and to investigate the in vitro inflammatory effects of different metabolic insults on human prostatic myofibroblast cells isolated from BPH patients (hBPH), reporting the results of two recently published preclinical and clinical multicentre studies.[9-10]

MATERIAL AND METHODS

Study Population and Design

Two consecutive cohorts of 271 patients treated with simple prostatectomy for BPH, were retrospectively selected. Height, weight, waist circumference (WC) and blood pressure, were measured and Body mass index (BMI) was calculated. Blood samples were drawn in the morning for determination of blood glucose, total cholesterol, HDL cholesterol and triglycerides.

Open transvesical prostatectomy (OP) or transurethral resection of prostate (TURP) were performed as previously reported.[11-12] Surgical specimens (taken by at least three different sites of the adenomatous tissue) were collected with sterile procedure, and used for both histological examination and inflammatory definition.

Assessment of LUTS, BPH Features, MetS and Characterisation of Prostatic Inflammatory Infiltrates

LUTS were measured by the International Prostate Symptom Score (IPSS) within one month from surgery. Meanwhile, prostate diameters (AP: antero-posterior; CC: cranio-caudal; LL: latero-lateral) were measured by TRUS and prostate volume was calculated using the ellipsoid formula ($AP \times CC \times LL \times \pi/6$), while maximum and average flow rate (Qmax, Qave) were obtained by uroflowmetry before surgery.

MetS was defined according to the criteria published by the International Diabetes Federation (IDF) & American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI)[13], and was based on single blood values (e.g. fasting glucose levels, lipid profiles).

All surgical specimens were examined on hematoxylin eosin-stained sections by two independent pathologists, blinded of clinical information. Samples were investigated for the presence of an inflammatory infiltrate, according to the classification of chronic prostatitis (CP-CPPS) of the National Institutes of Health.[14] The grading methods were based on an "inflammatory score" (IS). Moreover, the resulting destruction of the glandular epithelium due to the massive inflammatory infiltration was considered as a further marker of flogosis: "glandular disruption" (GD).[15] In addition, we investigated the in vitro inflammatory effects of metabolic insults on myofibroblastic hBPH, using three different primary human prostatic myofibroblast cultures obtained from three patients undergoing suprapubic adenomectomy for BPH (hBPH) as control hBPH cells, as previously described.[10]

RESULTS

Overall, 271 patients treated with simple prostatectomy for BPH were enrolled in the first study (clinical) and 244 in the second (preclinical), as 27 patients were excluded. Eighty-six men (31.7%) were affected by MetS. In particular, 46 (17.0%) presented with 3/5 parameters of

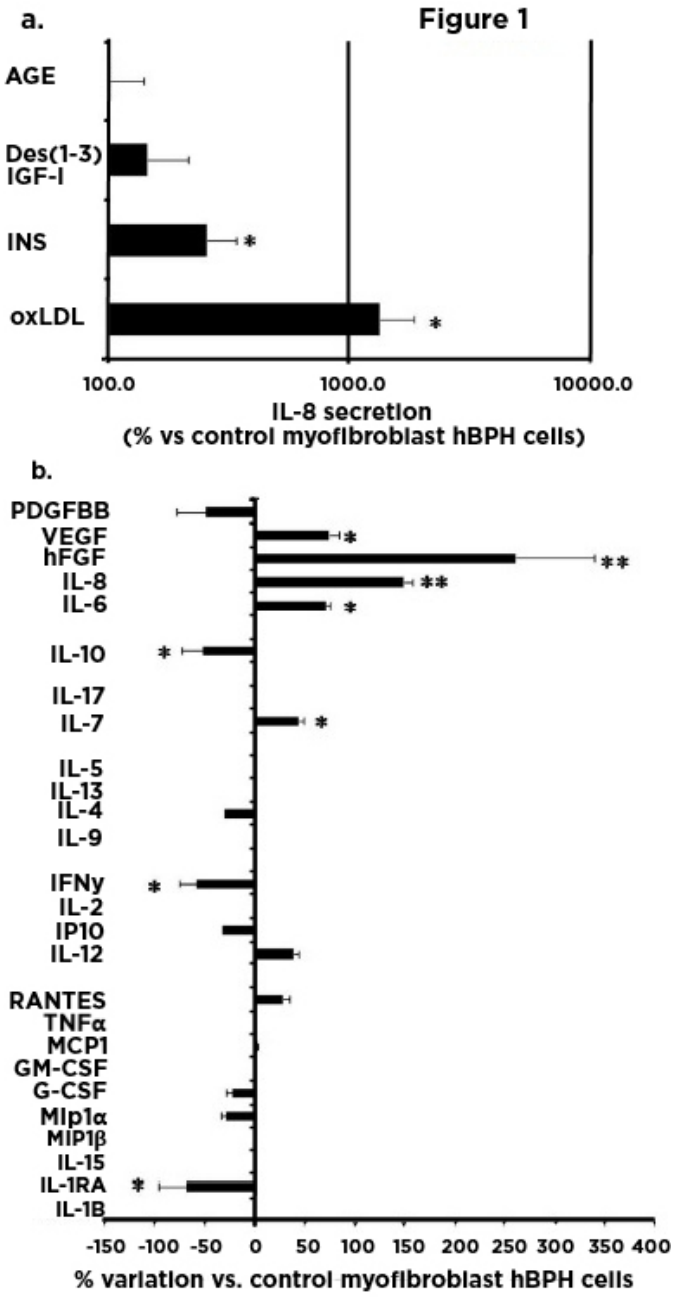

Figure 1. Panel a: Effect of different metabolic factors on IL-8 secretion by myofibroblast hBPH cells in a preliminary experiment.
Panel b: Effect of oxLDL treatment on cytokine/chemokine/growth factors secretion by myofibroblast BPH cells. (Adapted from Vignozzi et al.[10]).

MetS, 34 (12.5%) 4/5 and 6 (2.2%) 5/5.

Prostatic volume and AP diameter were significantly and positively associated with the number of MetS parameters, even after adjustment for age and 5-alpha reductase inhibitor's consumption (p=0.023 and p<0.0001, respectively). No correlation between MetS and the other diameters was observed (CC: p=0.198; LL: p=0.757). Patients fulfilling criteria for MetS (≥3 factors) had, on average, a prostate volume >60 cm3 (63 ± 27.39) and AP diameter >45 mm, those not fulfilling criteria had, on average, a prostate volume of 58cm^3. Among MetS parameters, only increased triglycerides and reduced HDL-cholesterol were associated with an increased risk of having a prostatic volume>60 cm3 (HR=3.268, p<0.001).

GD has been detected in 77/245 (31.4%) of cases. The presence of prostatic inflammation was demonstrated in all cases. The IS significantly increased as a function of MetS components (Figure 1), and patients with MetS had significantly a higher IS as compared to the rest of the sample (4.5±1.3 vs. 4.1±1.1; p=0.04). A significant positive correlation between the presence of MetS and the IS was observed (age and 5-alpha reductase inhibitor–adjusted HR: 1.250 [1.001–1.1561], p=0.049). Accordingly, each incremental unit of IS significantly increased the risk of having MetS, even after adjustment for age. Among MetS components, only dyslipidemia (reduced HDL cholesterol and elevated triglycerides) was significantly associated with elevated IS. Both IS and GD were correlated with total IPSS score, even after adjusting for age and BPH medical therapies (p=0.008 and p=0.050, respectively). In particular, a significant association between obstructive IPSS sub-scores and both IS (adj. r=0.166, p=0.011) and GD (adj. r=0.152, p=0.020) was observed, while irritative sub-scores were not correlated either with IS and GD.

Interestingly, we found that exposing myofibroblast hBPH cells to oxLDL (25 µg/ml, for 24 hours) significantly increased levels of a series of proinflammatory factors promoting BPH cell growth, such as IL-8, IL-6, bFGF, and VEGF. Secretion of the T cell growth factor IL-7 also significantly increased. Among the different factors, oxidised low-density lipoprotein (oxLDL) showed the highest secretion of IL-8 (>10-folds) – a surrogate marker of prostate inflammation – as well as IL-6, and bFGF (Figure 1 a and b).

DISCUSSION

These studies demonstrated the existence of an association among MetS features, prostate enlargement and prostate inflammation. We speculate that both conditions can have a relevant impact on LUTS severity in men with histologically proven BPH.

The progressive growth of the prostate in men with BPH, with the consequent modification of glandular profile into an oval, rounded shape, is mainly dependent on the increase of AP diameter.[16]

In our population of BPH men treated with simple

prostatectomy for severe LUTS, both prostate volume and AP diameter were progressively increasing as a function of MetS components. Interestingly, the fulfilling of the diagnostic criteria for MetS (simultaneous presence of at least three components) was associated with a pathological prostate volume and/or a pathological AP diameter. The strong association between MetS, in particular dyslipidaemia, and the AP diameter suggests that MetS is also associated with a modification of prostate shape which can lead to a compression of the prostatic urethra, with the consequent deterioration of voiding function.

A wealth of recent studies have indicated that prostate chronic inflammation is not only a common finding in BPH[17,18] but also plays a primary role in triggering prostatic cells overgrowth.[19-20] This notion mainly stems from preclinical studies, which have provided a great deal of information about an association between MetS and LUTS.

From a pathophysiological standpoint, dyslipidemia is the best recognised pro-inflammatory factor among all the others MetS features, leading to inflammation and pro-atherogenic remodelling of the vascular wall. Accordingly, among the metabolic factors tested (insulin, an IGF-1 analog, advanced glycation end product and oxLDL), only insulin and oxLDL induced a significant increase in IL-8 secretion, which was at least six-folds higher with oxLDL than with insulin. Interestingly, oxLDL was able to stimulate IL-8 secretion at a level similar to that achieved with TNFα, a well-known potent inflammatory trigger,[8,23] used in the study as positive control. This suggests that oxLDL could play a broad inflammatory effect on myofibroblast prostatic cells.

In our population, MetS was not only associated with an increased prostate volume and AP diameter, but also with a severe intraprostatic inflammation, and among MetS features, reduced HDL and increased triglyceride levels seem to be better predictors of prostatic inflammation than the other components of MetS. These observations substantiate the intriguing hypothesis that MetS could boost a chronic inflammation-driven prostate overgrowth. This is particularly relevant given that MetS is an emergent epidemic, and a potentially preventable or reversible, health condition.

Moreover, from a clinical point of view, the presence of a severe inflammatory pattern, leading to the disruption of the normal glandular arrangement, is the only determinant for a higher risk of LUTS deterioration.

CONCLUSION

The presence of MetS was associated with a substantial increase of prostate volume and a concomitant modification of prostate shape, associated with a selective increase of anterior posterior diameter. The presence of MetS, and in particular dyslipidemia, can be of importance for the development of a remarkable inflammation of the prostatic tissue, which could be a predictor, or even a driver, of BPH progression in men with severe LUTS.

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