Introduction: Metabolic syndrome (MetS) is a complex cluster of metabolic and cardiovascular risk factors and its features include: insulin resistance, central obesity, dyslipidemia (hypertriglyceridaemia, low serum high-density lipoprotein, cholesterol), and hypertension (1). Several studies have suggested that having MetS itself or some of its components could increase the risk of benign prostate hyperplasia (BPH) / lower urinary tract symptoms (LUTS) and the chronic inflammation correlated to MetS has been proposed as the putative link between these diseases. Phosphodiesterase type 5 inhibitors (PDE5i) are recognized as an effective treatment of BPH related LUTS but the mechanisms for LUTS improvement remains unclear. Recent studies revealed that the different LUT tissues represent a potential targets of PDE5i suggesting the role of PDE5 in counteracting prostatic inflammation associated with MetS.

Aims: In the present study, we investigate whether PDE5i could blunt inflammation in the human prostate.

Methods: We evaluated the anti-inflammatory effect of two selective PDE5i, tadalafil and vardenafil, on myofibroblasts isolated from BPH patients and exposed to different inflammatory stimuli (TNFα, oxidized Low-Density Lipoprotein, oxLDL, Advanced Glycation End products, AGE, IGF1) using IL8 secretion as readout. For IL8/IP10 quantification cell supernatants were analyzed with a specific ELISA assay. The RNA expression was evaluated by quantitative RT-PCR using 18S ribosomal RNA subunit as the reference gene for normalization.

In addition, histological analysis of inflammatory cell infiltrates in prostaticctomy specimens from BPH patients (n=44) enrolled in a randomized, double blind, placebo controlled study aimed at investigating the efficacy of vardenafil (10 mg/day, for 12 weeks) on LUTS/BPH, and its correlation with pre-operative MetS features, were also performed.

Preclinical Study

Clinical Study

Table 1. Demographic characteristics of patients population

<table>
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<tr>
<th>MetS</th>
<th>Placebo</th>
<th>Vardenafil</th>
<th>Placebo</th>
<th>Vardenafil</th>
<th>Overall</th>
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<tr>
<td>Age (yr)</td>
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<td>BMI (kg/m²)</td>
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<tr>
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</table>

Fig 1: PDE5 inhibitors blunt TNFα-induced inflammatory response in myofibroblast NHP.
Panel a: NHPH cells were cultured for 24 h with serum-free medium alone (control) or supplemented with TNFα 10 ng/mL for 5 h. Panel b: The effects of preincubation with tadalafil (100M, 1nM) or vardenafil (10M, 1nM) on expression of inflammatory and fibroblast-to-myofibroblast transition markers genes in NHPH cells treated with TNFα (10 ng/mL, 6h).

Fig 2: Tadalafil and vardenafil inhibit TNFα-induced secretion of IL-8 and IP-10.
NHPH cells were stimulated with TNFα (10 ng/mL for 5 h) with or without preincubation with tadalafil (100 nM for 1 h), vardenafil (10 nM for 1 h), (panel a) or in the PKG assay. Sp-8-BrE-cGMP (10 μM, 1 h). (Semi-b)

Fig 3: Effect of tadalafil and vardenafil on IL-8 secretion induced by oxLDL.
NHPH cells were cultured for 24 h with serum-free medium alone (control) or oxLDL (25 ng/mL) and preincubated with tadalafil (100 nM, 1 h), vardenafil (10 nM for 1 h), or Sp-8-BrE-ET-cGMP (8b cGMP, 10 μM, 1 h) and then with or without the PKG inhibitor KT 5823 (10 μM).

Fig 4: Effect of tadalafil and vardenafil on IL-8 secretion induced by AGE.
(a) Des (1-3) IGf: NHPH cells were cultured for 24 h with serum-free medium alone (control) or advanced glycation and products (AGE, 100 ng/mL). Panel a: or Des (1-3) IGf (1-IGf, 100 ng/mL, panel b) with or without preincubation with tadalafil or vardenafil (100 nM, 10 h or 1 h, respectively).

Fig 5: Effect of tadalafil and vardenafil on oxLDL receptor (LDX-1) expression.
NHPH cells were stimulated with TNFα (10 ng/mL for 5 h) with or without preincubation with tadalafil or vardenafil (100 nM, 10 h for 1 h, respectively).

Fig 6: Association between inflammatory score (a) and anti-CD45 positivity (b).
Inflammatory score (b, white bars) and anti-CD45 positivity (black bars) in prostate specimens as a function of the MetS.

Fig 7: Association between fibrinogen (panel a) and tgluglycerides levels, anti-CD45 positivity in prostate specimens.

Conclusions: Our data demonstrate that either tadalafil or vardenafil blunt inflammatory response induced by metabolic, as well as inflammatory stimuli, likely via the activation of cGMP/PKG signaling. The ability of PDE5i in counteracting prostatic inflammation associated with MetS and in particular to dyslipidemia, add new insights into the comprehension of the mechanism of action of PDE5 inhibitors in alleviating LUTS in MetS patients. Clinical studies specifically addressing this point are urgently needed.