**Introduction:** In the male, metabolic syndrome (MetS) is associated with an increased risk of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS). A recently established rabbit model of high fat diet (HFD)-induced MetS showed hypogonadism and the presence of prostate gland alterations, including inflammation, hypoxia and fibrosis.

**Aim:** The present study investigated whether HFD-induced MetS might also alter bladder structure and function. Testosterone (T) and the farnesoid X receptor (FXR) agonist INT-747, were evaluated for possible effects on HFD bladder rabbits.

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**Analysis of RhoA/ROCK hyperactivity, fibrosis (muscle/fiber ratio), inflammation and hypoxia in bladder from experimental rabbits**

**Effects of HFD and treatments on RhoA/ROCK signalling in rabbit bladder**

**Figures A and B**

Inhibiting CD45-positive cells in HFD bladder sections. Bladder sections from experimental groups (A–D, urothelial layer; E–H, muscular wall) immunostained with anti-CD45 antibody. Sections from RD (A and E), HFD + T (C and G), and HFD + INT (D and H) rabbits were negative. HFD bladder sections showed the presence of rare infiltrating CD45-positive inflammatory cells (arrows) in both urothelial layer (B) and muscular (F) wall.

**Figures C and D**

FXR mRNA was highly expressed in rabbit bladder and positively associated with visceral fat increase. Hypoxia probe positivity was revealed in hypoxic cells (pO2 < 10 mm Hg) of bladder transverse sections (A–D, urothelial layer; E–H, muscular wall) by a monoclonal antibody (magnification 10×).

**Figures E and F**

Hypoxia probe positivity was revealed in hypoxic cells (pO2 < 10 mm Hg) of bladder transverse sections (A–D, urothelial layer; E–H, muscular wall) by a monoclonal antibody (magnification 10×).

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**Conclusions**

Both treatments prevented some MetS features (glucose intolerance and visceral fat increase), thus suggesting that their effects on bladder could be ascribed to an improvement of the metabolic and/or hypogonadal state. However, a pathogenic role for hypogonadism has been ruled out as GnRH analog-induced hypogonadal rabbits, fed a regular diet, did not show any detectable bladder alterations. In addition, INT-747 did not revert the MetS-induced hypogonadal state. FXR mRNA was highly expressed in rabbit bladder and positively associated with visceral fat increase.

**FXR immunolocalization in rabbit bladder and effect of INT-747 on PDEGF-induced migration of smooth muscle cells isolated from rabbit bladder (rBSCM)**

**Figures A and B**

FXR immunopositivity was localized in both the endothelial and smooth muscle cells of the vascular bed (arrows) and stromal space (arrowheads), while urothelial layer was negative (asterisks; magnification 5×). (B) Enlarged representative image shows FXR immunolocalization to bladder muscular compartment (magnification 20×).

**Conclusions**

FXR-related MetS features are associated to bladder derangements, which are ameliorated by testosterone or INT-747 administration. INT-747 showed the most marked effects in countering MetS-related RhoA/ROCK overactivity, thus opening novel therapeutic opportunities for this drug.