Androgenic to Estrogenic Switch in the Prostate Gland of Overweight Patients

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BACKGROUND

- The steroid 5-α reductase type 2 (SRD5A2) is critical for prostatic development and growth. Strategies to block SRD5A2 using 5-α reductase inhibitors (5ARI) remain a mainstay in the treatment of benign prostatic hyperplasia (BPH).
- However, one-third of men are resistant to 5ARI therapies. We previously showed that body mass index (BMI) correlates with increased SRD5A2 gene promoter methylation and decreased protein expression in men with symptomatic BPH. We have demonstrated that there is an **"androgenic to estrogenic switch" when SRD5A2 is absent in the prostate gland.**
- Here we wished to identify whether obesity is associated with the androgenic to estrogenic switch in human prostate tissue.

METHODS

- Prostate specimens were collected from 35 patients who underwent transurethral resection of the prostate for symptomatic BPH at Massachusetts General Hospital.
- Medical records were reviewed to retrospectively collect clinical and pathological data. Patients were categorized by BMI as lean (less than 25 kg/m2), and overweight (25 kg/m2 or greater). Use and duration of alpha-blockers and/or steroid 5-α reductase inhibitors (5ARIs) was assessed.
- Methylation of SRD5A2 promoter was assessed using Methylated CpG Island Recovery Assay (MIRA).
- Prostatic levels of testosterone, dihydrotestosterone (DHT) and estradiol were measured by HPLC-MS.

RESULTS

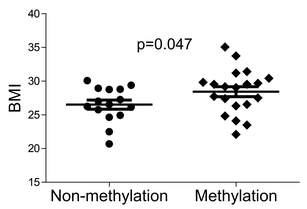

Fig. 1. Increased BMI was significantly correlated with methylation of SRD5A2 gene promoter in prostatic tissues. Non-Methylation: n=15; Methylation: n=20.

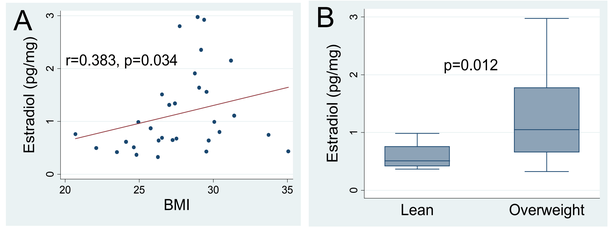

Fig. 2. (A) Prostatic estradiol was correlated with BMI. (B) The prostatic estradiol levels in overweight group was significantly higher than in lean group. Lean group: n=8; Overweight group: n=27.

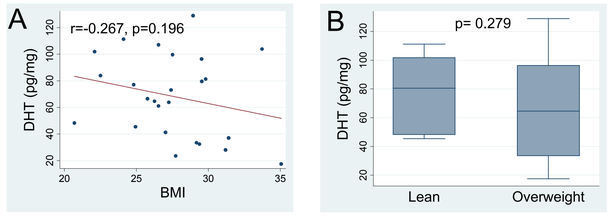

Fig. 3. (A) Prostatic DHT was negatively correlated with BMI, however, not statistically significant (p=0.196). (B) The prostatic DHT levels were not significantly different between overweight group and lean group. Lean group: n=8; Overweight group: n=27.

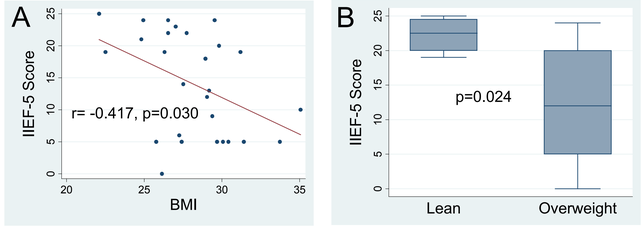

Fig. 4. (A) IIEF-5 score, International Index of Erectile Function Questionnaire score, was negatively associated with BMI (p<0.05). (B) IIEF-5 score in overweight group was significantly lower than in control lean group, which demonstrates that obesity may be associated with decreased sexual function. Lean group: n=8; Overweight group: n=27.

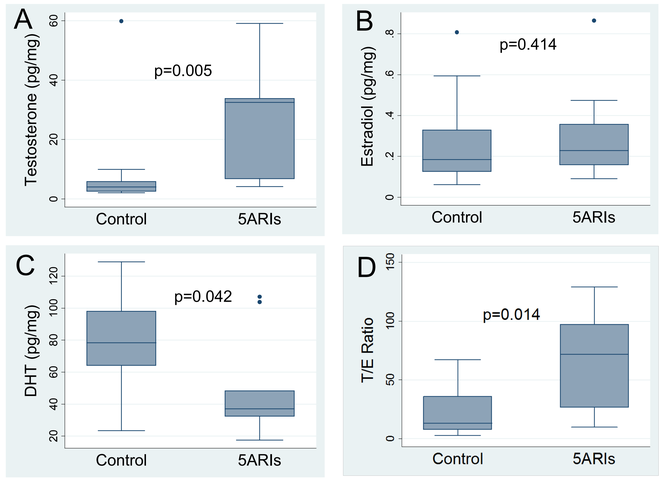

Fig. 5. The prostatic hormonal milieu was changed with 5ARIs therapy. Treatment with 5ARIs dramatically increased the levels of prostate testosterone (A), decreased the levels of DHT (C), and increased the ratio of testosterone/estradiol (T/E) in the prostate specimens (D). Treatment with 5ARIs did not significantly affect levels of estradiol (B). Control group: n=19; 5ARIs group: n=16.

CONCLUSIONS

- There is an androgenic to estrogenic switch in the prostate glands of overweight patients.
- Somatic epigenetic silencing of SRD5A2 changes the prostatic hormonal milieu, and may modulate prostatic homeostasis and growth.
- Targeting the estrogenic signaling may serve as an effective treatment strategy in subset of overweight BPH patients who do not express SRD5A2.

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