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Estrogen Reverses the Atrophic Effects of Hypogonadism on the Rat Urethra

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Background

- Hypogonadism is associated with worse clinical outcomes in artificial urinary sphincter (AUS) surgeries[1], likely related to decreased periurethral vascularity[2]
- Testosterone replacement therapy (TRT) is not an option in hypogonadal men on androgen deprivation therapy
- Estrogen, which has been demonstrated in male urethral tissue[3], has pro-angiogenic properties[4] and has shown to accelerate healing in hormone deprived models[5]
  - Could estrogen replacement therapy (ERT) be an alternative to TRT in hypogonadal men?

Research Objective

- To evaluate whether estrogen supplementation restores deficient periurethral vascularity in the hypogonadal rat urethra

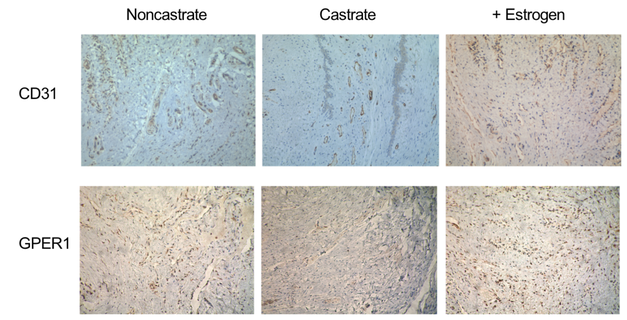
Methods

- Translational study approved by Institutional Animal Care and Use Committee of Northwestern (Protocol #IS00004702)
- 36 male Sprague-Dawley Rats split into three groups (Table 1):
  - NC: 12 noncastrated rats
  - C: 12 castrated rats
  - E: 12 castrated, estrogen supplemented rats (estradiol valerate 1mg/kg q2w)
- Half of each group underwent urethroplasty surgery (C or S suffix)
- At 8 weeks following surgery, urethral tissue examined using IHC:
  - CD31 – vessel marker
  - GPER1 – membrane-bound estrogen receptor

Table 1: Intervention Allocation

	Noncastrate Cohort		Castrated Cohort		Estrogen Cohort	
	NCC	NCS	CC	CS	EC	ES
Surgical Castration			x	x	x	x
Estrogen Supplementation					x	x
Urethroplasty Surgery		x		x		x

Figure 1: IHC Staining and Expression Levels



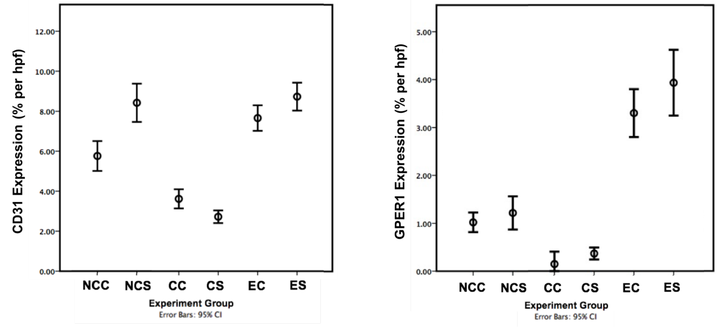
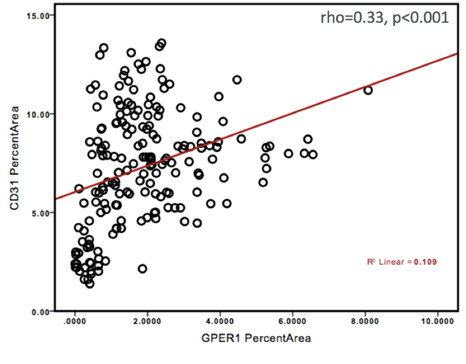


Figure 2: Correlation between GPER1 and CD31



Results

- CD31 Expression (Figure 1):
  - EC had greater expression than both NCC and CC (p<0.001):
    - EC: 7.6% NCC: 5.9% CC: 3.6%
  - ES and NCS had similar expression (p=0.34), both greater than CS (p<0.001)
    - ES: 8.7% NCS: 8.2% CS: 2.8%
- GPER1 Expression (Figure 1):
  - EC had greater expression than NCC (p<0.001)
    - EC: 3.3% NCC: 1.0%
  - ES had greater expression than NS (p=0.005)
    - ES: 3.9% NCS: 1.2%
  - CC and CS with virtually no expression
- GPER1 positively associated with CD31 expression (r=0.33, p<0.001) (Figure 2)

Conclusions

- In castrate rats, estrogen supplementation restored periurethral vascularity to the level of, or greater than, expression seen in noncastrate control rats
- Increased vascularity was associated with increased GPER1 expression
  - This suggests GPER1 is involved in the tissue response to estrogen supplementation *in vivo* in the male rat urethra
- These findings provide a basis for employing ERT as an alternative to TRT in hypogonadal men with prostate cancer in order to optimize surgical outcomes in men at high risk for AUS erosion

References

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4. Trenti, A., S. Tedesco, C. Boscaro, et al., *Estrogen, Angiogenesis, Immunity and Cell Metabolism: Solving the Puzzle.* Int J Mol Sci, 2018. **19**(3).
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