

Analyses of the vitamin D axis in serum and prostate tissues from African American and Caucasian men reveals that ancestry associates with differences in local regulation of the active hormone in the prostate

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Background: African American (AA) men are disproportionately affected by prostate cancer (PCa), with 60% higher incidence and twice the mortality rate compared to European American (EA) men. Vitamin D deficiency has not only been linked to increased PCa aggressiveness and mortality; it is also more prevalent in the AA population. Therefore, it has been hypothesized that Vitamin D deficiency may contribute to the disparity in incidence and mortality of PCa between AA and EA men. All of the studies to date have relied on serum levels of 25-hydroxyvitamin D₃ (25D) to evaluate vitamin D status. However, prostate cells are capable of local production of the active hormone, 1 α ,25(OH)₂D₃ (1,25D), as they express the 1 α -hydroxylase enzyme.

We hypothesized that African American men have differences in the prostatic vitamin D axis and response. The vitamin D axis was investigated in clinical samples from African American and European American PCa patients.

Methods: Serum, whole blood, and frozen prostate tissue were obtained from 57 PCa patients (AA n=29, EA n=28) via a tissue biorepository. The percentage of West African ancestry was determined by single-nucleotide polymorphism (SNP) analysis. The levels of vitamin D precursor (25D) and active hormone (1,25D) were measured in the serum and tissue by LC-MS-MS. Gene expression analysis was assessed on RNA isolated from laser-capture micro-dissected epithelium from 26 patients.

Results: The serum concentrations of 25D were significantly lower in AA men (95% CI, 16 - 23 ng/mL) compared to EA men (95% CI, 28-38 ng/mL), which emulated previous studies. Unexpectedly, prostatic concentrations of 1,25D were significantly *higher* in AA men (95% CI, 27-40 pg/mL) compared in EA men (95% CI, 18-28 pg/mL) whereas prostatic 25D was lower in AA men. Gene expression analysis of laser-capture micro-dissected epithelium showed a significant increase in the vitamin D receptor, VDR, in AA. The protein megalin, which imports serum 25D into cells was inversely correlated with vitamin D in AA only. As well, serum and prostatic levels of 25D correlated whereas serum and tissue 1,25D did not, suggesting local production of 1,25D from 25D rather than passive diffusion of 1,25D

Conclusions: There are two major findings of our study; 1) prostate tissue levels of vitamin D metabolites contrast the serum levels in men of African Ancestry, 2) 1,25D is produced locally in the prostate from imported 25D rather than passive diffusion into the tissue. **Systemic vitamin D deficiency in AA may lead to a compensatory response within the prostate to increase local levels of 1,25D via increased import and increased sensitivity via the VDR receptor. Moreover, our findings highlight the paucity of knowledge about the regulation of vitamin D status within tissues and the impact this may have on health and disease.**

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