Dutasteride and 5α-reductase type 1 activity: for androgens only?

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Background and Aim

- Three 5α-reductase (5α-R) isoenzymes are described (5α-R1-3)
- The role of 5α-R1 in physiological or pathological states is not clear
- 5α-R2 deficiency causes XY pseudohermaphroditism
- 5α-R3 deficiency causes neurological problems
- Urine steroid profiling (USP) by Gas-Chromatography Mass-Spectrometry (GC-MS) is effective in demonstrating 5α-R activity
- In the context of diagnosis of 5α-R2 deficiency significantly reduced excretion of 5α- compared with 5β-reduced steroid metabolites are seen
- These 5α-/5β-ratios are split into four: two androgen metabolite ratios, androsterone (A) to aetiocholanolone (Ae) and 11β-hydrpxyandrosterone (11OHA) to 11β-hydroxyaetiocholanolone (11OHAe)
- ...and two cortisol metabolite ratios, allo-tetrahydrocorticosterone (aTHB) to tetrahydrocorticosterone (THB) and allo-tetrahydrocortisol (allo-THF) to tetrahydrocortisol (THF)
- Dutasteride and finasteride are 5α-R inhibitors
- Finasteride use strongly inhibits 5α-R2 and to a lesser degree 5α-R1, USP in finasteride shows close concordance with 5α-R2 deficiency
- Dutasteride is a dual inhibitor and inhibits 5α-R1 60-fold compared to finasteride, USP on these individuals is not currently described
- **AIM:** to compare USP of finasteride and dutasteride against normal controls and individuals with 5α-R2 to investigate whether there are significant changes in excreted urinary steroid metabolites when 5α-R1 is inhibited in addition to 5α-R2

Method

- Retrospective case-control study using USP data compiled from samples submitted to our departmental database
- Three study groups formed: genetically confirmed 5α-R2 deficient patients (n=28), finasteride use (n=6) and dutasteride use (n=2) – compared with matched controls (n=36)
- Data analysed for significance with Mann-Whitney U test

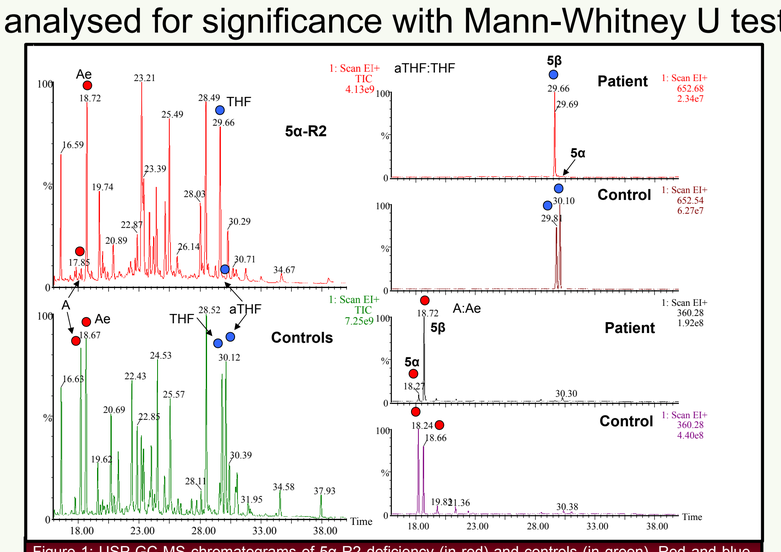

Figure 1: USP GC-MS chromatograms of 5α-R2 deficiency (in red) and controls (in green). Red and blue dots demarcate the 5α/5β androgen and corticosteroid metabolites respectively, individual molecules are labelled – chromatograms on right demonstrate isolated examples of 5α/5β ratios.

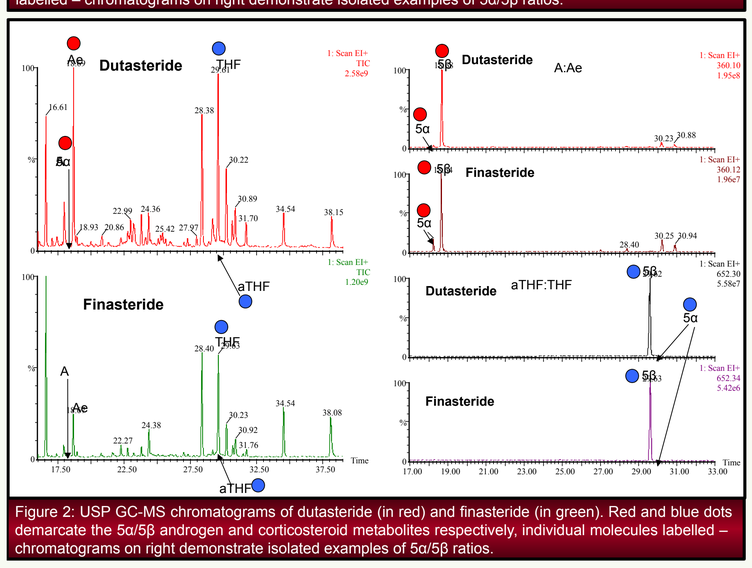

Figure 2: USP GC-MS chromatograms of dutasteride (in red) and finasteride (in green). Red and blue dots demarcate the 5α/5β androgen and corticosteroid metabolites respectively, individual molecules labelled – chromatograms on right demonstrate isolated examples of 5α/5β ratios.

Results

- Results summarised in box-and-whisker plots (figures 3-5)
- Controls showed higher 5α-/5β-ratios for androgen and corticosteroid metabolites – some overlap seen between controls and 5α-R2 deficiency in 11OHA:11OHAe ratio, all differences significant
- 5α-R2 deficiency and finasteride had range overlap in all four ratios, differences were not statistically significant
- Dutasteride and 5α-R2 deficiency had no range overlap in androgen metabolite ratios that was statistically significant, but gross overlap in corticosteroid ratios

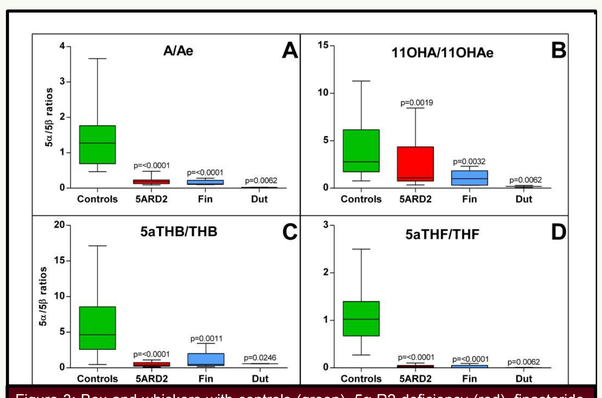

Figure 3: Box-and-whiskers with controls (green), 5α-R2 deficiency (red), finasteride (blue) and dutasteride (black) compared with p-values comparing study groups to controls written above respective plots. A and B show androgen 5α-/5β-metabolite ratios with C and D showing corticosteroid 5α-/5β-ratios

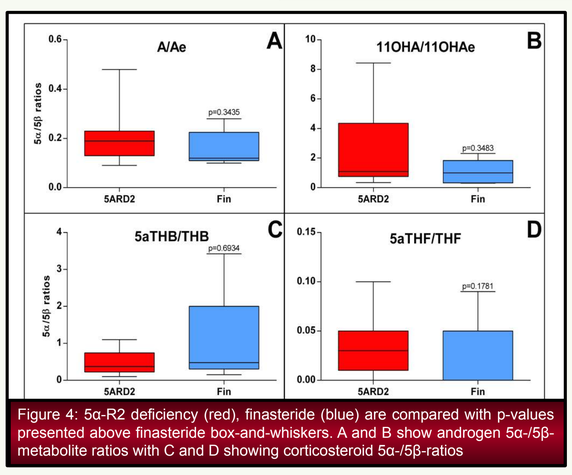

Figure 4: 5α-R2 deficiency (red), finasteride (blue) are compared with p-values presented above finasteride box-and-whiskers. A and B show androgen 5α-/5β-metabolite ratios with C and D showing corticosteroid 5α-/5β-ratios

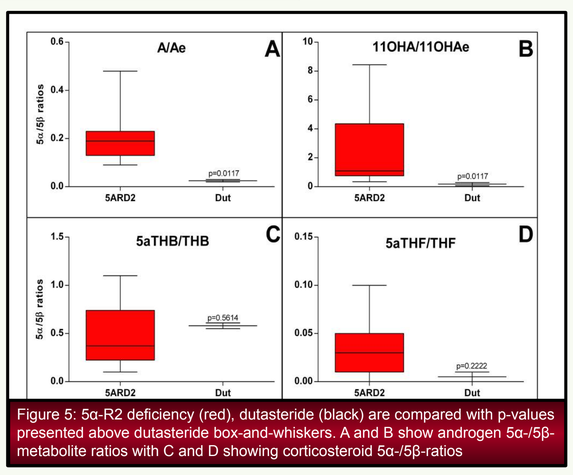

Figure 5: 5α-R2 deficiency (red), dutasteride (black) are compared with p-values presented above dutasteride box-and-whiskers. A and B show androgen 5α-/5β-metabolite ratios with C and D showing corticosteroid 5α-/5β-ratios

Conclusions

- We confirm that 5α-R2 deficiency and finasteride produce similar USP, with corticosteroid metabolites (aTHB:THB and aTHF:THF) being the main ratios affected, supporting the expectation that 5α-reduction of corticosteroids is more dependent on 5α-R2 activity
- We show there is a statistically significant reduction in androgen 5α-/5β-metabolite ratios (A:Ae and 11OHA:11OHAe) in dutasteride compared to 5α-R2 deficiency where 5α-R1 is inhibited in addition to 5α-R2, with the implication that 5α-R1 has a significant role in androgen catabolism
- This may include 5α-reduction of testosterone and dihydrotestosterone which may explain why the measuring the ratio of these androgens in the serum of patients with 5α-R2 deficiency can have a low diagnostic sensitivity
- There is evidence from animal studies that supports 5α-R1 having an involvement in androgen metabolism, including knockout studies that demonstrate derangement of sex steroids – there may be potential for similar pathological states in humans exhibiting similar USP to those seen in dutasteride

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