EP728

Women with idiopathic intracranial hypertension have a distinct andro-metabolic signature compared to polycystic ovary syndrome and simple obesity

Punith Kempegowda[2], Michael O'Reilly[2], Catherine Hornby[1], Hannah Botfield[1], Angela Taylor[2], Beverley Hughes[2], Jeremy Tomlinson[3], Wiebke Arlt[2] and Alexandra Sinclair[1]

[1] Neurometabolism, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK
[2] Centre of Endocrinology, Diabetes and Metabolism, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK
[3] Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), University of Oxford, Oxford, UK
Correspondence: p.kempegowda@bham.ac.uk

Background

Idiopathic Intracranial Hypertension (IIH)

- Disorder characterised by raised intracranial pressure of unknown aetiology.
- Up to 94% of IIH patients are young, obese women.

Androgen Pathway

•Testosterone and dihydrotestosterone are the most potent androgens, produced by gonads and adrenal glands but can also be produced through peripheral conversion.

•While aldo-keto reductase enzyme AKR1C3 catalyses testosterone production, 5α reductase plays an important role in breakdown of these androgens (Figure 1)

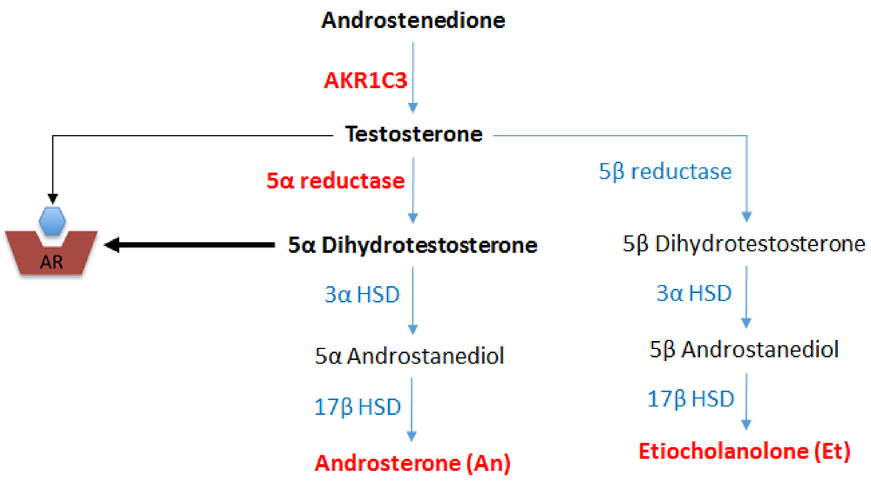

Figure 1: Androgen synthesis and metabolism. 5α reductase is a rate limiting step in androgen breakdown and hence urinary An/Et and 5αTHF/THF ratio helps measure androgen load.

IIH and PCOS

- PCOS is characterised by hyperandrogenism, primarily raised androstenedione, and increased systemic 5α reductase activity.
- Prevalence of PCOS in IIH patients is 39-57%, higher than the prevalence of PCOS in the general population (9-18%).
- Both conditions share similar phenotype of young, obese women.

Objective

To assess androgen metabolism in women with IIH in comparison to women with PCOS and healthy obese females.

Methodology

- 25 patients with IIH were compared to age and BMI matched 31 women with PCOS and 15 with simple obesity.
- Women with IIH were studied before and after weight loss intervention.
- All IIH patients had active disease (papilloedema and lumbar puncture pressure > 25cmCSF and had secondary causes including venous sinus stenosis excluded.
- All participants underwent comprehensive metabolic phenotyping and steroid profiling.
- Serum and 24-hour urinary androgens were measured by liquid chromatography-tandem mass spectrometry and gas chromatography/mass spectrometry respectively.
- Urinary steroid profiles were correlated with clinical parameters of IIH severity.

Results

	PCOS	IIH	Controls	P-value
Age (years)	32±8	34±9	35±4	0.285
BMI (kg/m^2)	38±5	38±5	35±4	0.146

Table 1: Comparison of age and BMI between IIH, PCOS and healthy obese females. Results in mean±SD format. All subjects were females.
There was statistically no significant difference between the three groups.

	IIH Baseline	IIH Post-weight loss	Mean difference	P value
LP Pressure	37.8±4.7	29.7±4.8	8.3±4.1	0.000
Papilloedema	136.2±46.3	111.3±27.4	27.3±34.6	0.001
Visual acuity	0.09±0.4	0.02±0.2	0.1±0.2	0.033
Headache severity	58.2±8.9	46.7±10.1	11.5±10.4	<0.001
HOMA IR	3.2±3.0	1.3±1.1	1.3±2.3	0.016
DHEA	18.6±9.3	16.4±12.6	0.5±12.2	0.847
Androstenedione	7.5±7.4	3.9±2.4	0.4±1.4	0.259
Testosterone	1.7±0.8	1.6±0.3	0.3±0.5	0.006
An/Et ratio	1.4±0.7	1.2±0.7	0.4±0.5	0.003
5αTHF/THF ratio	1.0±0.5	0.9±0.5	0.3±0.4	0.003

Table 2: Comparison of effects of weight loss on IIH and androgen profile. Results in mean±SD format. There was significant reduction in testosterone synthesis with simultaneous reduction in markers of 5α reductase activity. (HOMA IR- Homeostatic model assessment insulin resistance, LP- Lumbar puncture, DHEA-Dehydroepiandrosterone)

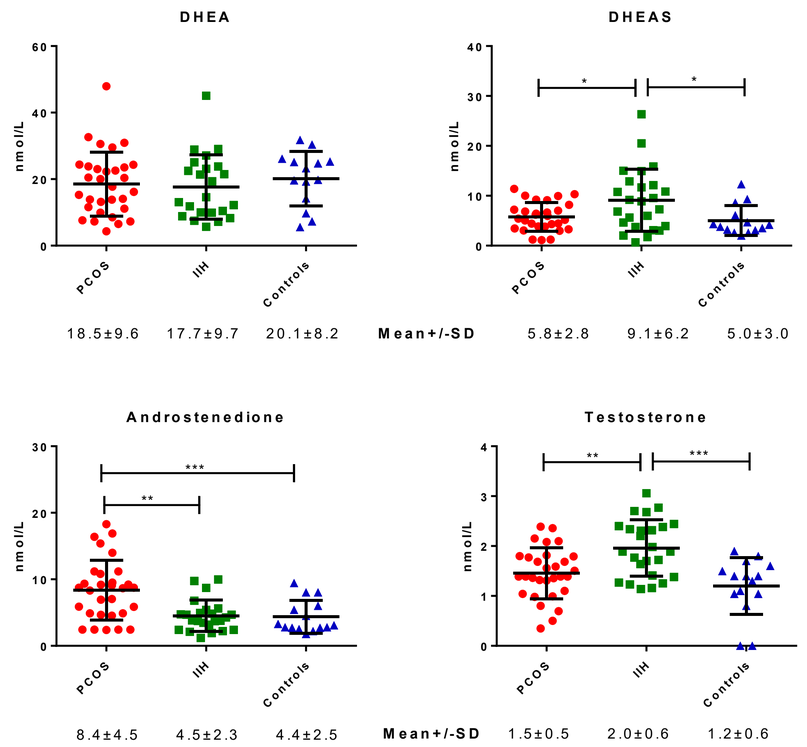

Figure 2: Comparison of androgens between the three groups. Serum testosterone and DHEAS were significantly higher in IIH. Androstenedione was not elevated in IIH (but was in PCOS).
Reference range in Mean±SD format. * p<0.05, ** p<0.01, *** p<0.001

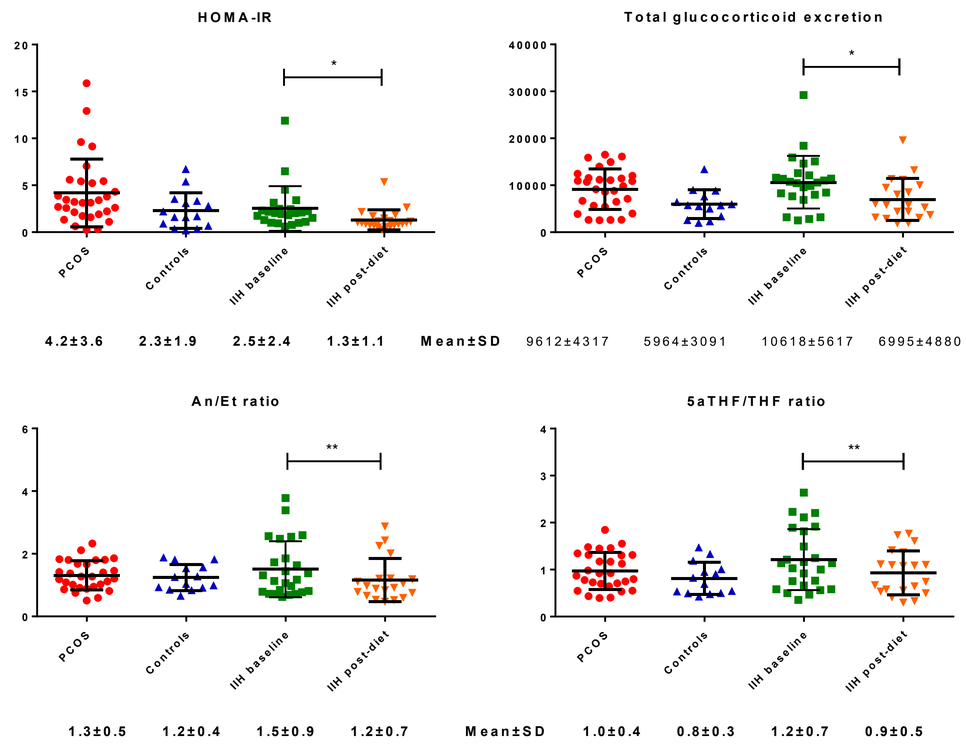

Figure 3: Post-intervention, reduced excretion of total glucocorticoid metabolites and markers of 5a reductase activity was noted in the IIH group following weight loss.
Reference range in Mean±SD format. * p<0.05, ** p<0.01

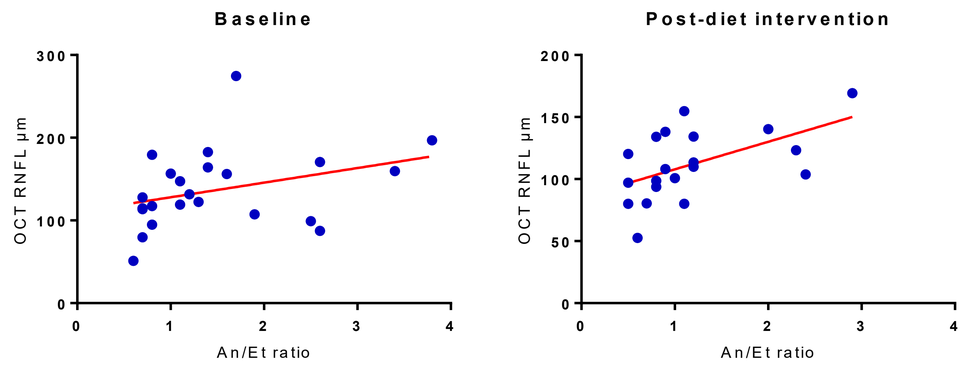

Figure 4: An/Et ratio correlated significantly with markers of papilloedema (optical coherence tomography (OCT) average retinal nerve fibre layer thickness (RNFL)) in IIH both at baseline (R=0.47, p=0.02) and post-intervention (R=0.56, p=0.0096)

Conclusion

- IIH is characterised by increased testosterone but not androstenedione.
- In IIH, Testosterone and 5α-reductase activity falls following therapeutic weight loss alongside a significant reduction in disease activity (intracranial pressure and papilloedema).
- IIH maybe characterised by increased AKR1C3 activity, as evidenced by increased serum testosterone relative to androstenedione, which may improve after weight loss.

References

1. Sinclair, Alexandra J., et al. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. BMJ. 2010
2. O'Reilly M, et al. Understanding androgen action in adipose tissue. J Steroid Biochem Mol Biol. 2014