Longitudinal changes in the plasma metabolome across estradiol and anti-androgen gender-affirming hormone therapy: A randomized double-blind trial of spironolactone and cyproterone acetate.

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Background:
The plasma metabolome undergoes extensive changes during puberty, with surges in circulating sex hormones thought to play a key role. Despite gender-affirming hormone therapy (GAHT) being a cornerstone of transgender care, longitudinal changes in the plasma metabolome across estradiol and anti-androgen feminizing GAHT have not been well described. Plasma metabolites are useful disease biomarkers and studying these across GAHT is important for equitable healthcare.

Methods: In this longitudinal double-blind trial, transgender women initiating feminizing GAHT (n=53) were randomized to cyproterone acetate or spironolactone. Blood samples were collected at baseline (pre-GAHT), and after three (3m) and six months (6m) of GAHT. The plasma metabolome was measured using the Nightingale NMR-based platform.

Results: Using mixed linear models, we identified numerous metabolites significantly changing across GAHT, with common and unique effects of the two anti-androgens. After 6m of GAHT, we identified 43 common metabolites significantly altered relative to baseline in both anti-androgen groups (adj p-val < 0.05), of which 25 (58.1%) belonged to the very low-density lipoprotein (VLDL) subclass and 12 (27.9%) belonged to the low-density lipoprotein (LDL) subclass, with all but one showing a decrease over time. The ApoB:ApoA1 ratio, a marker of cardiovascular risk, was also significantly decreased after 3m and 6m GAHT (relative to baseline) in both groups. In the cyproterone acetate group, we observed a unique decrease in several amino acids over time, with glutamine showing the most significant decrease after 3m and 6m relative to baseline. Glutamine was associated with prolactin levels, suggesting an interplay between these two markers.

Conclusion: Our results suggest an anti-atherogenic shift in the plasma metabolome across the first six months of feminizing GAHT, with cyproterone acetate having a unique effect on reducing plasma amino acids. This study provides novel insight into the metabolic signature across feminizing GAHT.