Dual 5-alpha reductase inhibition promotes hepatic lipid accumulation in man

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Background

Non-alcoholic fatty liver disease (NAFLD) is increasingly prevalent and is associated with significant morbidity and mortality. Both glucocorticoids (GCs) and androgens have been implicated in its pathogenesis. Tissue-specific availability of these hormones is controlled at a pre-receptor level by a series of enzymes including the A-ring reductases 5α-reductase type 1 (SRD5A1) and 2 (SRD5A2). These enzymes inactivate cortisol as well as activating testosterone to the more potent androgen dihydrotestosterone. SRD5A1 and SRD5A2 are both expressed in the liver with only SRD5A1 expressed in adipose. Several studies have highlighted a link between metabolic phenotype and 5α-reductase activity. The metabolic impact of inhibiting these enzymes with the dual inhibitor (Dutasteride) and selective SRD5A2 inhibitor (Finasteride) (both drugs commonly used for prostatic disease) has begun to be elucidated. Our study extends this observations to examine lipid metabolism within the liver and the mechanisms underlying these observations.

Methods

Twelve healthy male volunteers (mean age 36.3±4.4 years, body mass index (BMI) 26.6±1.2 kg/m^2) (LREC ref 12/WM/0122) were recruited. All were non-diabetic and not on medications that regulate GC metabolism Volunteers had a series of detailed metabolic investigations pre and post 3 weeks of treatment with either Dutasteride (0.5mg od) or Finasteride (5mg od). Investigations included hepatic magnetic resonance spectroscopy to evaluate intrahepatic lipid, 2-step-hyperinsulinaemic euglycaemic clamps incorporating stable isotopes with concomitant adipose tissue microdialysis to evaluate tissue-specific carbohydrate and lipid flux as well as an analysis of the serum metabolome using ultra performance liquid chromatography mass spectrometry. Serum and urinary steroids were analysed by liquid chromatography and gas chromatography respectively.

Results

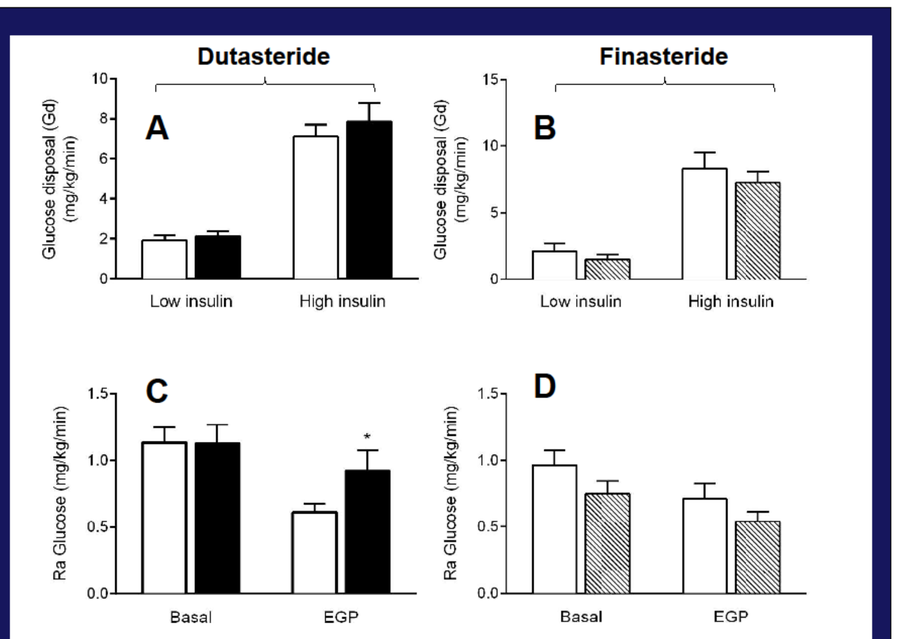


Figure 1. The effect of Dutasteride (a and c) and Finasteride (b and d) on glucose disposal (Gd) (a and b) and glucose production (Ra) (c and d). Open bars represent pre-treatment and filled bars represent the effect of 3-weeks of drug treatment (black=Dutasteride, shaded=Finasteride; * p<0.05 *vs.* pre-treatment).

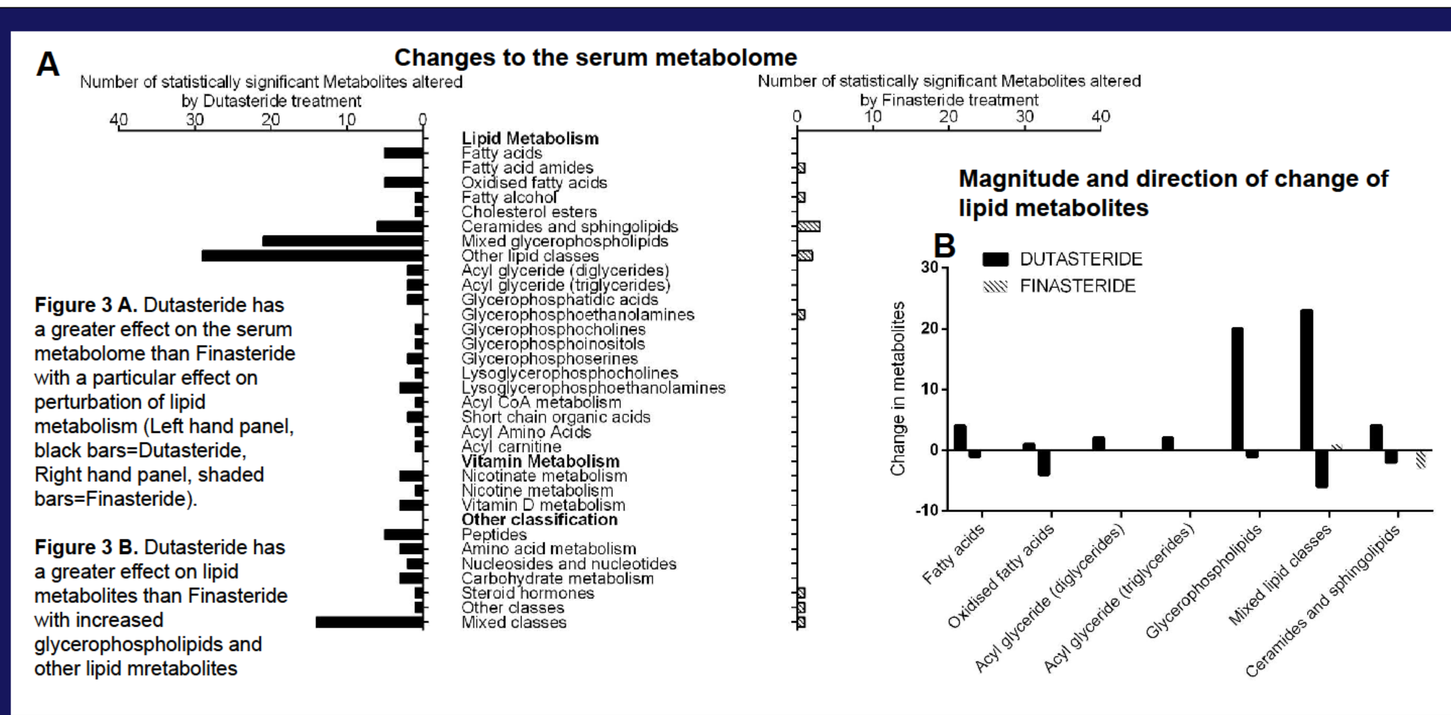
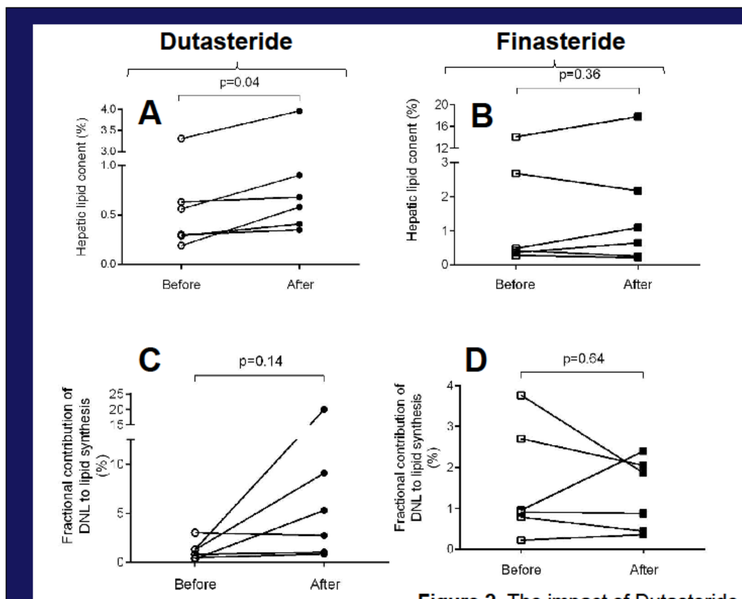


Figure 3 A. Dutasteride has a greater effect on the serum metabolome than Finasteride with a particular effect on perturbation of lipid metabolism (Left hand panel, black bars=Dutasteride, Right hand panel, shaded bars=Finasteride).

Figure 3 B. Dutasteride has a greater effect on lipid metabolites than Finasteride with increased glycerophospholipids and other lipid mretabolites



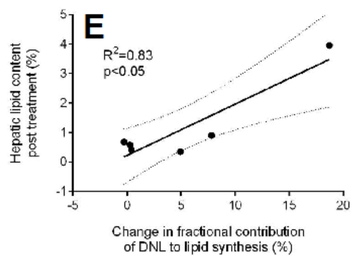


Figure 2. The impact of Dutasteride (a and c) and Finasteride (b and d) on hepatic lipid content % as measured by MRS (a and b) and *de novo* lipogenesis (DNL) as measured by deteurated water incorporation into plasma triglyceride palmitate (c and d). Open circles/squares represent pre-treatment and filled circles/squares represent the effect of 3-weeks of drug treatment (circles=Dutasteride, squares=Finasteride; * p<0.05 *vs.* pre-treatment). The change in rate of DNL is positively correlated with final liver lipid content after treatment with Dutasteride (e) but not Finasteride.

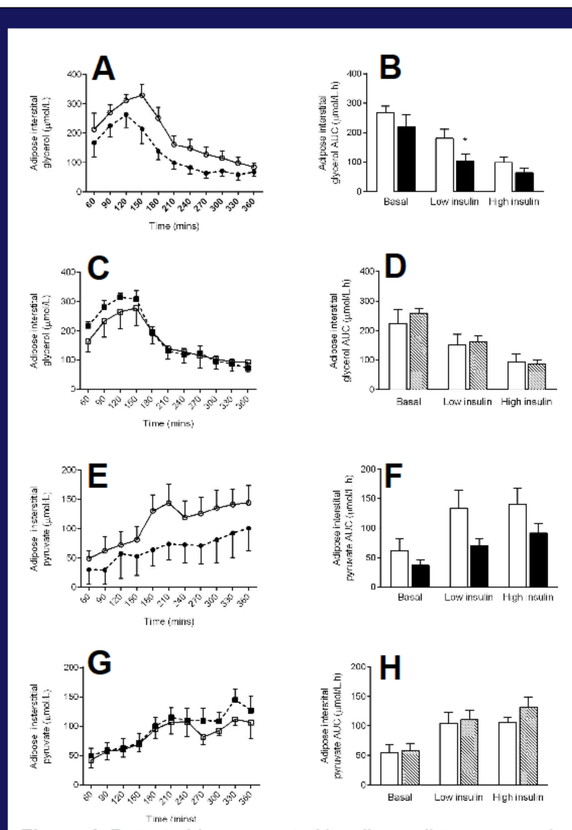


Figure 4. Dutasteride augmented insulin-mediate suppression of lipolysis in abdominal subcutaneous adipose tissue as measured by adipose interstitial fluid release of glycerol into the microdialysate (a and b). In contrast, Finasteride is without effect (c and d). Similarly, Dutasteride decreases insulin-stimulated pyruvate release into adipose interstitial fluid (e and f) whilst Finasteride is without effect (g and h). Data are presented across the duration of the hyperinsulinemic-euglycemic clamp (a, c, e and g) and also expressed as area under the curve (AUC) for the basal, low insulin and high insulin phases (b, d, f and h). Open circles/squares/bars represent pre-treatment and filled circles/squares/bars represent the effect of 3-weeks of drug treatment (circles or black bars=Dutasteride, squares or shaded bars=Finasteride; * p<0.05, **p<0.01 *vs.* pre-treatment).

Results: Neither agent had a significant effect on biochemical or anthropometric data. Dutasteride treatment was associated with a reduction in systolic blood pressure. Both agents caused a reduction in the 5α-reduced steroid metabolites (data not shown). Dutasteride but not Finasteride increased hepatic insulin resistance as measured by endogenous glucose production rate (**Figure 1**). Neither drug altered whole body insulin resistance measured by rate of infusion of glucose or M/I values (data not shown). Dutasteride and not Finasteride resulted in an increase in MRS hepatic lipid content and an increase in *de novo lipogenesis* (**Figure 2 A and B**), This change in DNL was positively correlated with hepatic lipid content. Dutasteride more markedly changed the profile of the fasting serum metabolome (123 *vs.* 11 metabolites altered) (**Figure 3 A**). The changes to the serum metabolome were dominated by changed within lipid metabolites (**Figure 3 B**). Dutasteride had a greater effect on interstitial release of glycerol and pyruvate as anticipated by the known tissue expression profile of SRD5A1 and 2.

Conclusion

In this study, Dutasteride treatment was associated with hepatic insulin resistance, hepatic lipid accumulation and decreased adipose lipid mobilisation without impacting upon peripheral insulin sensitivity. Dutasteride reduced lipolysis and increased lipogenesis pointing towards DNL as the source of lipid for the observed increase in hepatic lipid accumulation rather than from lipid mobilisation from adipose. The proposed detrimental effect of Dutasteride driving the hepatic phenotype is supported by the marked change seen in lipid metabolites from the serum metabolome. Given the prevalence of prescriptions of Dutasteride and Finasteride, as well as informing us regarding the pathogenesis, of NAFLD this data may provide clinical information that may influence the choice of 5α-reductase inhibitors.

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