Steroid Metabolomic Signature
of Liver Disease in Childhood Obesity

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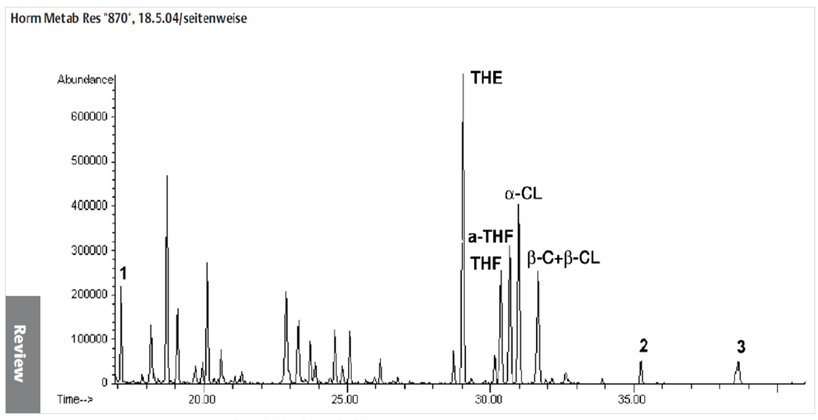
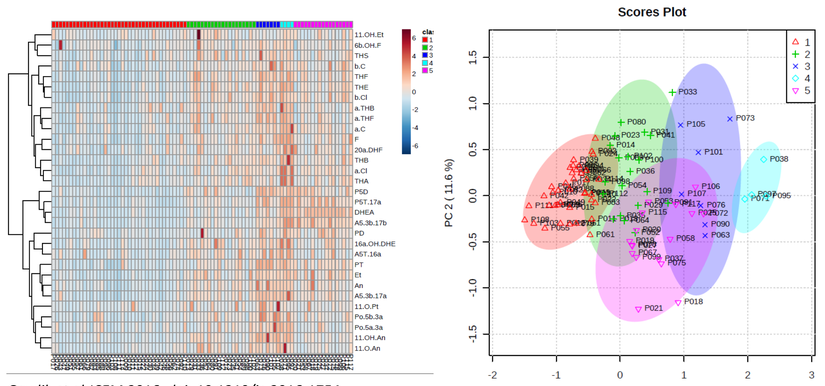
Context



Wudy & Hartmann. Horm Metab Res. 2004;36:415–22.

Steroid profile (chromatogram) defines **a subject's steroidal fingerprint.**



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A cluster of similar steroidal fingerprints related to a disease condition might be regarded as the **"steroid metabolomic disease signature".**

Purpose

Here, we compare the steroidal fingerprints of obese children with or without liver disease to identify the **'steroid metabolomic signature'** of childhood non-alcoholic fatty liver disease.

Material & Method

117 consecutive series of obese patients (BMI>97%)

Exclusion criteria: aged <8 years, patients with syndromic obesity, chronic diseases or during pharmacotherapy

85 patients with non-syndromic obesity (43 girls/F) 14.4 ± 2.3yrs (8.5-18 yrs)

Clinical / Chemical Phenotype: age; sex; BMI, z-score BMI (IOTF) ; ALT (s); abdomen US (hepatic steatosis features)

liver disease (L1) - 22 patients (7F/22M)	***N***	**no liver disease (L0) – 63 patients (36F/27M)**
as assessed by sonographic steatosis (S+) and/or elevated liver enzymes (ALT+)		no sonographic steatosis (S-) and no elevated liver enzymes (ALT-)
14.4 years	*mean age* p>0.05	14.1 years
2.82	*z-score BMI* p>0.05	2.67

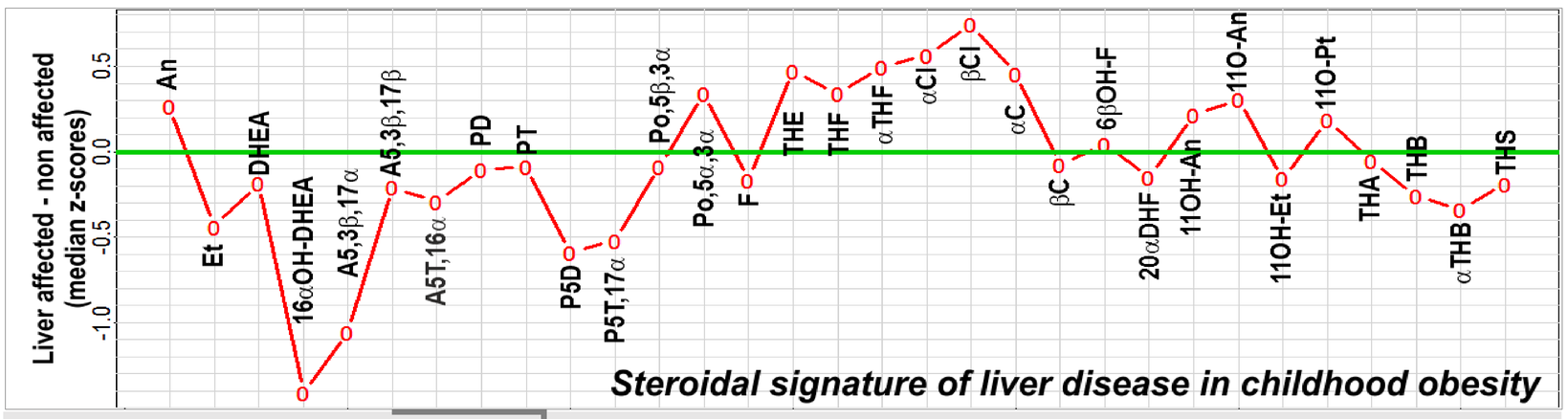
Steroidal "fingerprint" : samples from 24-h urinary collection

31 steroid metabolites were quantified by gas chromatography-mass spectrometry (GC-MS)

Quantities were z-transformed based on sex & age

The steroidal signature of the liver disease was generated as a difference of median profiles of L1 and L0 groups

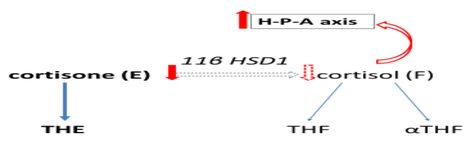
Results



L1 was characterized by high glucocorticoids and low androgens

Urinary steroid metabolites	comparison	*p*	
(THE+THF+αTHF)/PT	L1 > L0	*0.029*	→ L1: higher 21OHase activity
(THF+αTHF)/THE	L1 < L0	*0.01*	→ L1: lower 11β-HSD-I activity
α-cortolone	ALT+ > L0 or S+	*0.03*	
An/Et	ALT+ > ALT-	*0.001*	→ ALT+ : higher 5 α-reductase activity
F, THF, αTHF, α-C, THE, α-Cl, β-Cl DHEA, 16α-OH-DHEA, A5T-16α P5T-17α; THA, THB, αTHB (THE+THF+αTHF)/PT (THE+THF+αTHF)/Po5α3α	$L1^H$>$L1^L$ (PCA)	*<0.05* *<0.001*	→ 2 extreme subgroups of L1: $L1^H$ - high activation of HPA axix and higher 21OHase activity

L1- patients with liver disease; L0- patients without liver disease, $L1^H$ – subgroup of L1 with the extremly high elevation of all steroid metabolites (z-score >2SD); $L1^L$ – subgroup of L1 with the lowest concentration of steroid metabolites; PCA – principal component analysis



abbreviation	Urinary steroid metabolites	Origin of urinary steroid
AN	5α-Androstane-3α-ol-17-on (androsterone)	DHEA, androstenedione, testosterone
ET	5β-Androstane-3α-ol-17-on (etiocholanole)	DHEA, androstenedione, testosterone
DHEA	5-Androstene-3β-ol-17-on (dehydroepiandrosterone)	DHEA-sulfate
16α-OH-DHEA	5-Androstene-3β,16α-diol-17-one	DHEA-sulfate
A5-3β,17α	5-Androstene-3β,17α-diol	DHEA
A5-3β,17β	5-Androstene-3β,17β-diol (androstenediol-17β)	DHEA
A5T-16a	5-androstene-3β,16α,17β-triol (androstenetriol-16α)	DHEA-sulfate
PD	5β-Pregnane-3α,20α-diol (pregnanediol)	Progesterone
PT	5β-Pregnane-3α,17α,20α-triol (pregnanetriol)	17-hydroxyprogesterone
P5D	5-Pregnene-3β,20α-diol (pregnenediol)	Pregnenolone
P5T-17α	5-Pregnene-3β,17α,20α-triol (pregnenetriol-17α)	17-hydroxypregnenolone
Po-5β,3α	5β-Pregnane-3α,17α-diol-20-one (17a-OH-pregnanolone)	17-hydroxyprogesterone
Po-5α,3α	5α-Pregnane-3α,17α-diol-20-one	17-hydroxyprogesterone
F	4-Pregnene-11β,17α,21-triol-3,20-dione (cortisol)	cortisol
THE	5β-Pregnane-3α,17 α,21-triol-11,20-dione	cortisone
THF	5β-Pregnane-3α,11β,17α,21-tetrol-20-one	cortisol
αTHF	5α-Pregnane-3α,11β,17α,21-tetrol-20-one	cortisol
α-Cl	5β-Pregnane-3α,17α,20α,21-tetrol-11-one (α-Cortolone)	cortisone
β-Cl	5β-Pregnane-3α,17α,20β,21-tetrol-11-one (β-Cortolone)	cortisone
α-C	5β-Pregnane-3α,11β,17α,20α,21-pentol (α-Cortol)	cortisol
β-C	5β-Pregnane-3a,11b,17a,20β,21-pentol (β-Cortol)	cortisol
6β-OH-F	4-Pregnene-6β,11β,17α,21-tetrol-3,20-dione (6β-hydroxycortisol)	cortisol
20α-DHF	4-Pregnene-11β,17α,20α,21-tetrol-3-one (20α-dihydrocortisol)	cortisol
11-OH-AN	5α-Androstane-3α,11β-diol-17-one (11-hydroxy-androsterone)	Cortisol, 11-hydroxyandrostenedione
11-O-AN	5α-androstane-3α-ol-11,17-dione (11-oxo-androsterone)	Cortisol, 11-hydroxyandrostenedione
11-OH-ET	5β-androstane-3α,11β-diol-17-one (11-hydroxy-etiocholanolone)	Cortisol, 11-hydroxyandrostenedione
11-O-PT	5β-Pregnane-3α,17α,20α-triol-11-one (11-oxo-pregnanetriol)	21-deoxycortisol
THA	5β-Pregnane-3α,21-diol-11,20-dione(tetrahydro-11-dehydro-corticsterone)	Corticosterone
THB	5β-Pregnane-3α,11β,21-triol-20-one (TH-Ccorticosteron)	Corticosterone
α-THB	5α-Pregnane-3α,11β,21-triol-20-one (Allo-TH-Corticosteron)	Corticosterone
THS	5β-Pregnane-3α,17α,21-triol-20-one (tetrahydro-11-deoxycortisol)	11-deoxycortisol

Conclusion

These findings suggest decreased hepatic reduction of cortisone to cortisol in liver steatosis, which is compensated by activation of HPA axis and increased adrenal cortisol generation. It may provide ways for personalized medicine in obese children with liver disease.

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