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The circulating fingerprint revealed by targeted metabolomic as biomarker of metabolic impairment in female obesity

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BACKGROUND: **The comprehension of the network of metabolic processes may aid the understanding of the molecular pathways driving obesity and the related complications. However this is a hard task due to the large number of actors and their complex interplay. Multivariate analysis of metabolic profiling data (metabolomics) allows for variable selection and data dimension reduction, thus representing a useful statistic tool for highlighting the metabolic-impairments related specific pathways.**

METHODS: **We aimed at exploring by targeted metabolomic the circulating metabolite plasma profile in lean (NW, n=42; BMI: 18.5-24.9 kg/m^2) and age-matched overweight/obese (OB, n=37, BMI≥25.0 kg/m^2), drug-free adult overnight-fasted healthy women. Anthropometric, biochemical and hormonal data were collected. One-hundred-eighty molecules among aminoacids (AAs), acylcarnitines (AAc), phosphatidyl-choline (PCs) and lysophosphatidyl-choline (LysoPCs) and sphingomyelines (SMs) were quantified by the Absolute p180 LC-MS/MS Kit (Biocrates Life Science AG, Austria). BMI effect on metabolite profile was investigated by the orthogonal partial least squares-discriminant analysis (OPLS-DA), resulting in the selection of 39 metabolites [VIP>1.0 and |p(corr)|>0.5] driving the group separation (R^2X=0.485, R^2Y=0.638, Q^2Y=0.505, CV-ANOVA p<0.001). The association between the resulting 39 metabolite model and parameters of metabolic impairment was investigated by BMI-adjusted stepwise multiple regression analysis.**

RESULTS

VARIABLES	BMI<25	BMI≥25	P*
	n=42	n=37	
Age (years)	45.4 ± 1.97	46.5 ± 2.13	0.7677
Waist circ. (cm)	96.8 ± 1.08	115.0 ± 2.11	<0.0001
Hip circ. (cm)	77.0 ± 1.28	100.5 ± 2.23	<0.0001
BMI (Kg/m^2)	21.9 ± 0.280	32.1 ± 0.941	<0.0001
SBP (mmHG)	121.0 ± 2.37	130.8 ± 3.40	0.0178
DPB (mmHG)	78.8 ± 1.25	83.1 ± 1.79	0.0612
Menopause (n, %)	14 (33.33%)	10 (27.02%)	0.7148#
Glucose (mg/dl)	84.7 ± 1.32	92.3 ± 2.32	0.0083
Insulin (μU/dl)	5.93 ± 0.296	10.6 ± 0.974	<0.0001
HOMA-IR	1.11 ± 0.065	2.46 ± 0.257	<0.0001
Total Chol. (mg/dl)	183.9 ± 4.79	198.0 ± 5.31	0.0492
HDL (mg/dl)	65.0 ± 1.96	57.9 ± 3.16	0.0134
Triglycerides (mg/dl)	59.5 ± 3.34	96.0 ± 7.09	<0.0001
Creatinine (mg/dl)	66.2 ± 1.48	64.4 ± 2.07	0.3605
Uric acid (mg/dl)	3.65 ± 0.126	4.42 ± 0.133	<0.0001

Table 1: Anthropometrics and Biochemical features
Data are presented as mean ± SEM
**Log transformed, Student's T test*
#Fisher's exact test

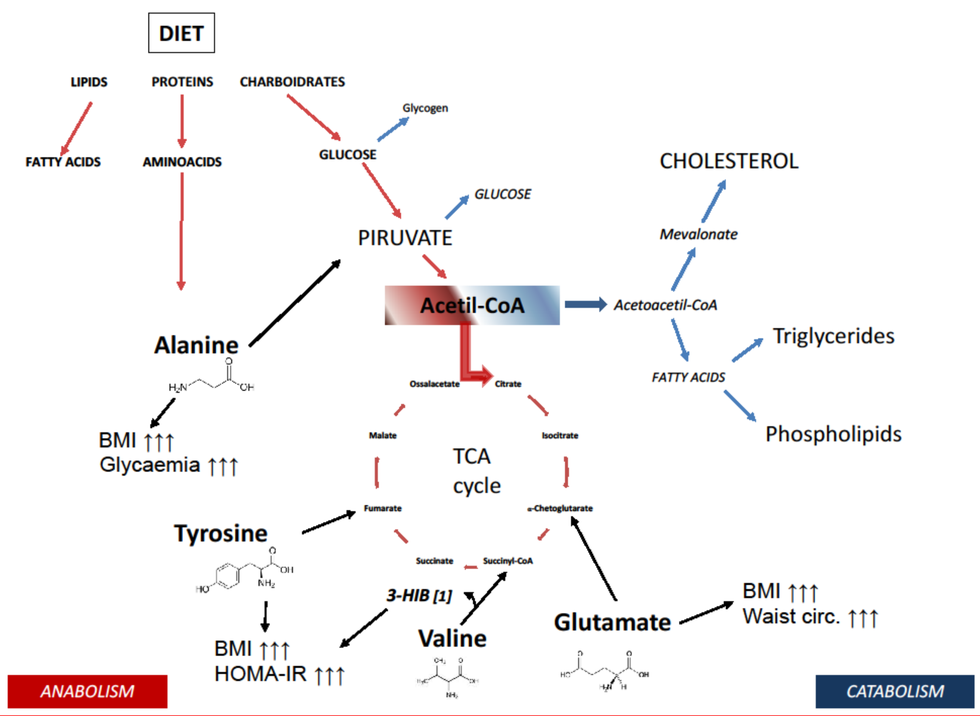
Outcome	Predictor	Class	relation	β	P
Waist Circ.	Glutamate	aminoacid	DIR	0.251	0.040
	Valine	aminoacid	DIR	0.393	<0.001
	PCaa C42:2	PCs diacyl	INV	-0.174	<0.001
	LysoPC C18:2	LysoPCs acyl	INV	-0.198	<0.001
Glycaemia	Alanine	aminoacid	DIR	0.441	0.025
	SM C18:0	SMs	DIR	0.505	0.008
	PCae C34:3	PCs acyl-alkyl	INV	-0.581	0.004
Insulin	Valine	aminoacid	DIR	0.306	0.002
	PCae C34:2	PCs acyl-alkyl	INV	-0.359	0.001
HOMA-IR	Tyrosine	aminoacid	DIR	0.337	<0.001
	PCae C34:2	PCs acyl-alkyl	INV	-0.350	0.001
Total Chol.	SM C18:0	SMs	DIR	0.352	0.008
	SM(OH)C22:1	HydroxySMs	DIR	0.227	0.024
HDL	Tyrosine	aminoacid	INV	-0.224	<0.001
	Valine	aminoacid	INV	-0.289	<0.001
	LysoPC C20:4	LysoPCs acyl	DIR	0.263	0.038
	PCae C34:3	PCs acyl-alkyl	DIR	0.506	<0.001
Triglycerides	PCaa C24:0	PCs diacyl	DIR	0.193	0.036
	PCaa C38:3	PCs diacyl	DIR	0.464	<0.001
	PCae C32:1	PCs acyl-alkyl	INV	-0.315	0.007
	PCae C36:3	PCs acyl-alkyl	INV	-0.389	0.012

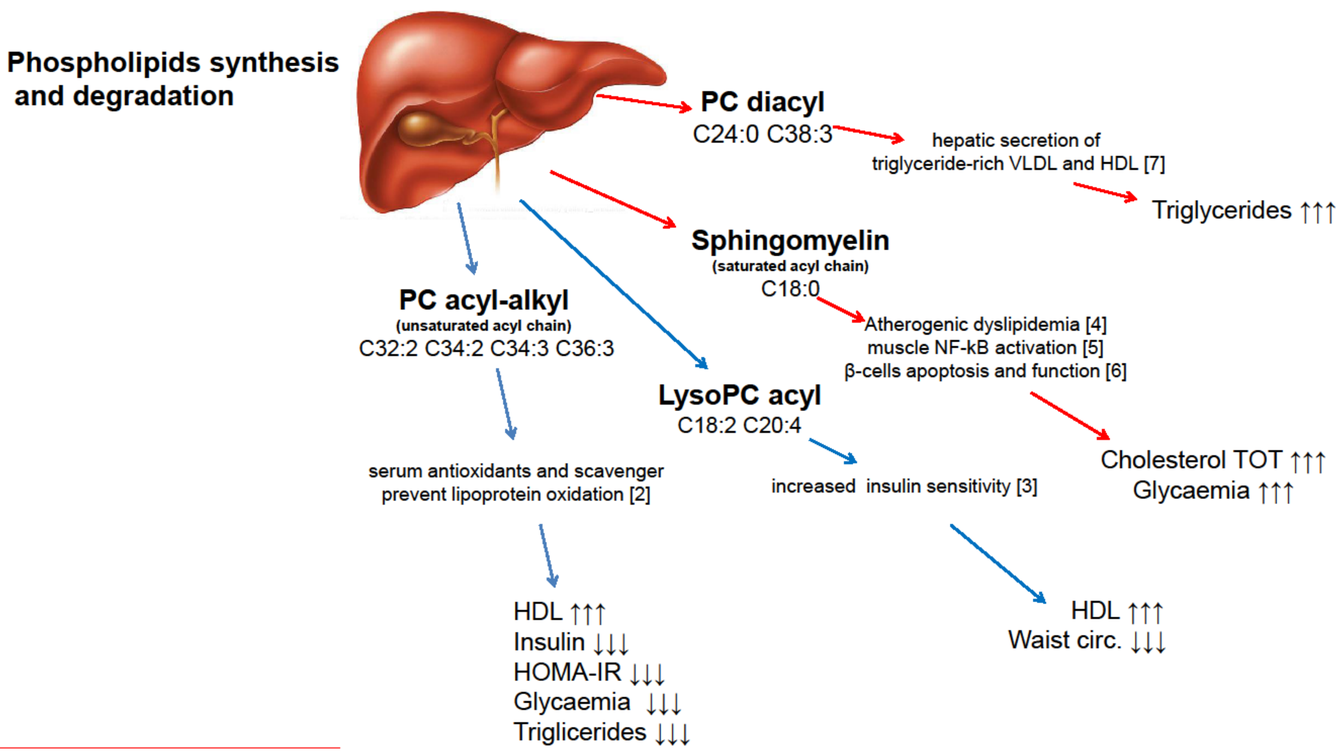
Table 3: BMI-adjusted stepwise multiple regression analysis.

VARIABLES	BMI<25	BMI≥25	P*
	n=42	n=37	
Alanine	328.0 ± 11.9	382.1 ± 16.7	0.0198
Glutamate	66.5 ± 3.90	91.5 ± 7.42	0.0005
Tyrosine	66.0 ± 2.13	73.6 ± 2.79	0.0449
Valine	219.7 ± 4.99	236.2 ± 5.28	0.0246
LysoPC acyl C18:2	35.3 ± 1.75	23.3 ± 1.45	<0.0001
LysoPC acyl C20:4	6.97 ± 0.324	6.15 ± 0.252	0.0664
PC diacyl C24:0	0.234 ± 0.012	0.270 ± 0.014	0.0308
PC diacyl C38:3	43.4 ± 1.95	53.2 ± 1.753	0.0002
PC diacyl C42:2	0.339 ± 0.014	0.291 ± 0.014	0.0130
PC acyl-alkyl C32:1	2.76 ± 0.091	2.45 ± 0.077	0.0139
PC acyl-alkyl C34:2	12.7 ± 0.507	9.81 ± 0.377	<0.0001
PC acyl-alkyl C34:3	8.19 ± 0.354	5.86 ± 0.264	<0.0001
PC acyl-alkyl C36:3	8.52 ± 0.336	6.90 ± 0.276	0.0005
SM C18:0	21.6 ± 0.729	23.1 ± 0.651	0.0983

Table 2: Metabolites levels : NW vs OB
Data are presented as mean ± SEM
**Log transformed, Student's T test*

Simplified representation of aminoacids energetic metabolism (left panel) and of proposed links between phospholipids and metabolic parameters (right panel) according to multiple regression analysis results.





CONCLUSION: **The targeted metabolomic approach allowed the identification of a specific metabolic fingerprint in female non-complicated obesity that should be further explored as early biomarker of dysmetabolism.**

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