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Blandine Comte, Béatrice Morio, Jean-Francois Martin, Emilie Chanseaume, Maud Alligier, C. Junot, Alain Paris, Bernard Lyan, Yves Boirie, Hubert Vidal, et al.

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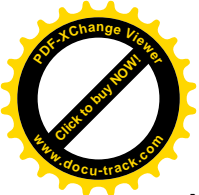
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## N° 34 Oral Presentation

### Session 7 – Optimizing phenotypic flexibility, physiological benefits and healthy ageing

#### Differences in metabolic trajectories and flexibility revealed by metabolomics during overfeeding in normal and overweight subjects

Comte, B , INRA UMR1019, Clermont-Ferrand, France  
Morio, B , INRA UMR1019, Clermont-Ferrand, France  
Martin, JF , INRA Plateforme d'Exploration du Métabolisme, Clermont-Ferrand, France  
Chanseau, E , INRA UMR1019, Clermont-Ferrand, France  
Alligier, M , INSERM U1060, Lyon, France  
Junot, C , CEA-LEMM, Gif sur Yvette, France  
Paris, A , INRA Metarisk, Paris, France  
Lyan, B , INRA Plateforme d'Exploration du Métabolisme, Clermont-Ferrand, France  
Boirie, Y , INRA UMR1019, Clermont-Ferrand, France  
Vidal, H , INSERM U1060, Lyon , France  
Laville, M , INSERM U1060, Lyon, France  
Pujos-Guillot, E , INRA Plateforme d'Exploration du Métabolisme, Clermont-Ferrand, France  
**Sébédio, JL , INRA UMR1019, Clermont-Ferrand, France**

Shifts in dietary pattern, food composition and processing as well as a modification in physical activity are linked to nutritional transitions. In the context of deleterious behavior, transition has led to an energy imbalance not only in the Western world but also in emerging countries with an increasing prevalence of overweight and obesity. Obesity is associated with increased risk of metabolic syndrome which is a complex disease involving dysregulation of several metabolic pathways. The purpose of the present work was to compare metabolic trajectories followed by free living non-obese overweight and lean subjects during a moderate weight gain induced by a lipid-enriched supplementation of the diet. Metabolomics allowed us determining early changes in metabolic signatures with indicators of metabolic alterations.

Thirty eight male adult subjects, 19 normal weight (BMI: 20-24.9 kg.m<sup>2</sup>, no family history of obesity; NW) and 19 overweight (BMI: 25-29.9 kg.m<sup>2</sup>, known family history of obesity; OW) were recruited and submitted for 56 days to an overfeeding protocol consisting in adding an excess of 3,300 kJ/d to their usual diet. Conventional anthropometric and metabolic parameters were measured over time. Plasma and urine samples were collected at different time points for an untargeted metabolomic approach. Deproteinized plasma and diluted urine samples were analyzed using UPLC-QToF-Micro mass spectrometer. Univariate (ANOVA) and multivariate (OSC-PLS) models were used to explore the kinetic differences between OW and NW subjects. Metabolite identifications were performed using public databases and complementary analyses on a LTQ Orbitrap Velos high resolution mass spectrometer. For most of the anthropometric, biochemical, metabolic parameters and for some plasma metabolomic data, the phenotypes were discriminated at any time of the kinetic. On the whole, plasma metabolite signatures evolve similarly in NW and OW subjects. In comparison with the NW, lower abundances of plasma highly unsaturated lysophospholipids were observed in OW while increased levels of saturated isomers occurred with the intervention in both groups. Urinary metabolomic profiles clearly evidenced different metabolic trajectories between groups, generally characterized in OW by an increase over time of short- and medium-chain acylcarnitines and bile acids. Changes in metabolic signatures induced by the overfeeding protocol occurred at different time points for the NW and OW volunteers. Therefore, the comprehensive metabolic profiling provided by metabolomics revealed a differential response to the nutritional intervention in urine metabolomes of NW and OW, indicating dissimilar metabolic flexibility. Changes with weight status of plasma and urine metabolites, mostly related to modifications in fatty acid  $\beta$ -oxidation and metabolism, and inflammation indicate a greater metabolic flexibility in NW subjects. In conclusion, this study demonstrates that untargeted metabolomics allows detecting subtle metabolic changes linked to differences in metabolic flexibility that were not evidenced by a classical approach.

Keywords metabolic trajectory; metabolomics; overweight; human nutritional intervention