Metabolic adaptations in insulin resistant and dyslipidemic minipigs ranging from lean to morbid obesity.

Authors: Imene Bousahba[1,2*], Jérémie David[1], Yves Guerin[1], Benoit Cohade[1], Didier Rémond[1], Nathalie Poupin[2] and Sergio Polakof[1].

[1]Université Clermont-Auvergne,INRAE,UMR1019,Unité Nutrition Humaine,Clermont-Ferrand, France.
[2]UMR1331 Toxalim,Université de Toulouse,INRAE,INP-Purpan,Toulouse,France.*imene.bousahba@inrae.fr

Introduction: Type 2 diabetes (T2D) is a silent and slowly progressive metabolic disease to which obesity is a major contributor and whose prevention could be significantly improved if individuals at risk could be identified earlier (1). Our aim is therefore to identify phenotypes that anticipate the onset of T2D in minipigs(2) for the determination of early metabolomics-based biomarkers of T2D. Methods: We fed four groups of minipigs (n=5-10) either on normal-fat or on a high-fat high-sugar (HFHS) diet during 2, 4 or 6 months. Body weight (BW), lean mass, fat mass (FM) and morphometric features were recorded. Biochemical, hormonal and inflammatory parameters were assessed on fasting plasma samples. Results and discussion: Based on multivariate statistical analysis, we observed that 4 different groups were differentiated, with 30% of the variance explained by both morphological (BW, FM) and clinical (total and HDL cholesterol, insulin, HOMA-IR and incretins) components, allowing to identify 4 distinct phenotypes: lean (LP), overweight (OWP), obese (ObP) and morbidly obese (MObP). Compared to the LP, we observed a BW increase of 2, 2.5, and 3-fold in the OWP, ObP and MobP respectively, mostly due to the FM accretion (4, 7 and 11-fold respectively). Concerning the clinical phenotype, insulin-resistance (IR) was already present in the OWP, which was further accompanied by a significant hyperinsulinemia ($p = 0.03$) that increases by 3.5-fold for the OWP, ObP, and MobP. Interestingly, IR affected rather lipid (2-fold increased free fatty acids) than glucose (steady glucose levels) metabolism. We also observed mild dyslipidemia with increased total cholesterol (1.3-fold) and HDL (2-fold) for all 3 phenotypes, as well as the incretin hormones (GLP-1, GIP) which actions are jointly responsible for 60% of insulin-secretion (GLP-1 $p=0.02$), preventing hyperglycemia. These variations are surprisingly maintained in the ObP and MObP despites of the strong weight and FM gain. The clinical phenotype was further completed by a rather pro-inflammatory pattern (slightly higher TNF-a, TGF-B) offset by a significant increase (3.7-fold) of IL-4 in the ObP, yet not confirmed in the MoBP. Conclusion: Our results show that in minipigs ranging from lean to morbid obesity, IR was rapidly installed and accompanied by dysregulated lipid metabolism, while hyperglycemia was prevented by improved incretin adjustments. This ability to regulate the metabolism in the presence of progressive concomitant BW gain and adiposity with a background of IR and mild dyslipidemia makes of this model an interesting tool for the ongoing early T2D metabolomics-based biomarker's discovery. References: 1. Chatterjee et al, *The Lancet*, 2017. 2. Koopmans et al, *European Journal of Pharmacology,* 2015.