FOOD AND NUTRITIONAL SCIENCES

University of Reading

Type 2 Diabetes drives metabolic changes in liver fingerprint

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Introduction

Type 2 Diabetes (T2D) is associated with insulin resistance (IR) and metabolic syndrome[1]. Nowadays, the world is facing a growing diabetes epidemic of devastating proportions, and its impact will be felt most severely in developing countries[2]. Mice homozygous for the diabetes spontaneous mutation (Leprdb) are obese around 3 weeks of age. They present a series of features such as uncontrolled rise in blood sugar and severe depletion of the insulin-producing beta-cells of the pancreatic islets conditioned by the genetic background[3,4]. This study aims to understand the metabolomic fingerprint of liver from diabetic and healthy individuals.

Material and Methods

- Two groups of control type (CT) and diabetic type (Db/Db) BKS.Cg-Dock7<m> +/+ Lepr<db>/ J female mice (n=8) were kept into an homogenous environment during 18 weeks.
- Body gain (BG) was measured on weekly basis for 18 weeks and liver biopsies were collected. Final body weight, liver and White Adipose Tissue (WAT) weight were measured.
- Liver NMR spectra were acquired on a Bruker Avance III 500 MHz NMR using a Magic Angle Spinning probe allowing acquisition of the metabolic fingerprints on intact biopsies.
- Statistical analyses were carried out on BG, liver relative weight and WAT relative weight. NMR spectra were pre-processed using MestReNova and analysed in Matlab using the Korrigan Toolbox.

Results

Body gain was significantly higher in diabetic animals ($p<0.01$), in particular during the first six weeks ($p<0.001$) when the animals increased the body gain between 1,100-65%.

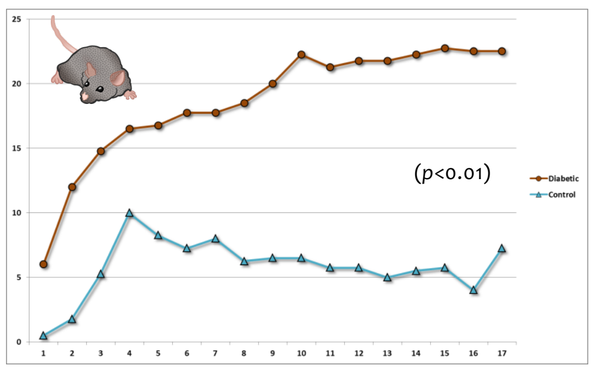

Figure 1- Body gain (BG) of diabetic (red) and control (blue) mice during the 17 time points. BG was significantly higher ($p<0.01$) in the diabetic group.

Relative liver weight was higher in healthy animals (13.6%) than in diabetic ones but there were not statistical differences. Conversely, relative WAT weight was significantly higher (434.78%) in the diabetic group ($p<0.001$).

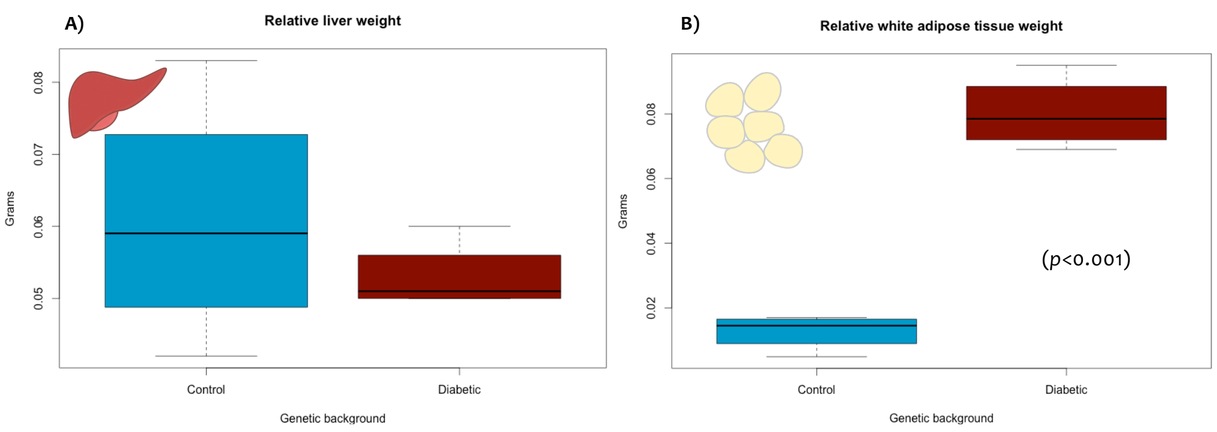

Figure 2- Relative liver weight (A) was 13.6% higher in control mice than in diabetic, although there were not statistical differences. Relative WAT weight (B) was higher (434.78%) in diabetic animals than in control ($p<0.001$).

Clusters were observed using Principal Component Analysis (PCA) on the overall population in response to the genetic background. Healthy animals (Figure 3, blue) had an increased HDL and phosphatydilcholine, while diabetic animals (Figure 3, red) had higher levels of VLDL and triglycerides.

Control animals showed a different metabolic profile for each lobe, while diabetic animals showed a very congregated metabolic profile.

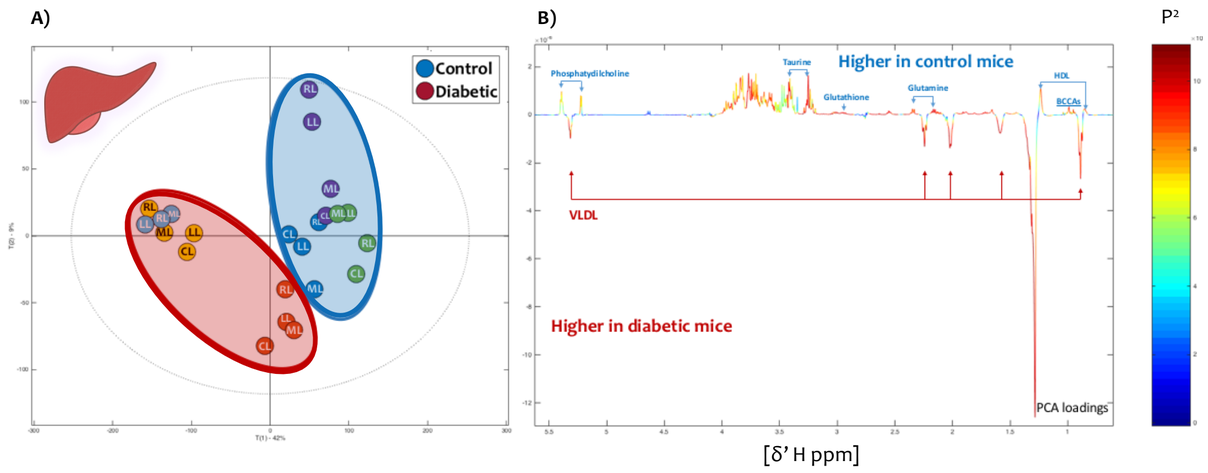

Figure 3- PCA shows clusters between control and diabetic mice (A). Each animal was individually dot coloured. Lobes from healthy animals (RL, Right Lobe, ML, Medium Lobe, LL, Left Lobe and CL, Caudate Lobe) were differentiated giving an unique metabolic profile while lobes from diabetic animals were congregated in what could indicate an absence of metabolic differentiation between lobes. Loading plots (B) shows the difference in the metabolic fingerprint.

O-PLS DA was conducted on the all samples using genetic background as an independent predictor. Models strength was 0.8288 (R^2Y) and 0.7105 (Q^2Y).

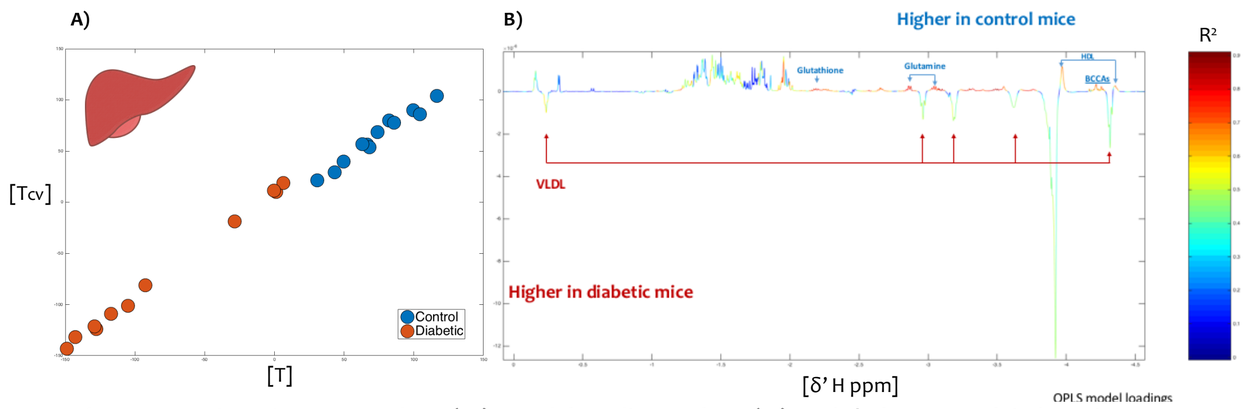

Figure 4- OPLS score plot (A) and loading plot (B). Db/Db were higher in VLDL and CT were higher in glutathione, glutamine and HDL.

Conclusion

BG was significantly higher ($p<0.01$) in diabetic individuals. Relative WAT weight was higher in diabetic ($p<0.001$) and metabolomics NMR analysis showed a clear differentiation between diabetic animals and control, with an increase of VLDL and triglycerides in diabetic individuals. Lobes differentiation in diabetic animals is reduced in comparison with controls animals, that showed a greater degree of metabolomics differentiation.

References

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