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Effect of a long-term high fat diet on metabolic health and oocyte quality of an outbred (Swiss) *vs.* inbred (C57BL/6N) mouse strain

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Maternal metabolic disorders like obesity and diabetes type II are known to affect reproductive physiology, ultimately leading to poor fertility. The oocyte and embryo are extremely vulnerable during the periconceptional period to metabolic stressors leading to disappointing fertility results. Most mouse model research regarding obesity and Western type diets has been performed on the inbred C57BL/6 strain. However, inbred strains are often linked with decreased fertility. Relying only on inbred strains might also limit translation to human (outbred) physiology. To further explore this, we compared the inbred C57BL/6N to an outbred Swiss strain. Five week old Swiss (N=30) and C57BL/6N (B6) (N=29) mice were fed a control (CTRL) or a high fat (HF) diet for 13 weeks. Diets differed in percentage of fat (10% *vs.* 60%). Body weight gain, serum profile (NEFA, cholesterol and triglycerides) and oocyte quality were studied. Mature oocytes were collected after hormonal stimulation (I.P. injection of 10IU PMSG followed by 10IU hCG 48h later). To study oocyte quality, Bodipy (lipid droplets), JC-1 (mitochondrial membrane potential (MMP)) and Cell-Rox Deep Red (ROS) stainings were performed, as well as transmission electron microscopy (TEM) to examine mitochondrial structures. All data were analyzed using T-test. In comparison with the CTRL group, HF diet increased body weight with 18.09% and 27.87% in Swiss and B6, respectively. HF significantly increased blood cholesterol levels (103.5 mg/dL *vs.* 143.1 mg/dL in Swiss mice, 141.8 mg/dL *vs.* 185.4 mg/dL in B6 mice) in both strains, and tended to increase blood NEFAs (P=0.053) and triglycerides (P=0.075) only in Swiss and not in B6 mice. Oocytes collected from HF-diet group contained a larger total volume of lipid droplets (P<0.05) in both strains compared to controls. MMP and ROS were significantly increased (P<0.05) in oocytes of Swiss mice, not B6 mice, fed a HF diet. TEM images from HF-oocytes showed mitochondria with abnormal morphology, low electron density and rose petal appearance, resulting in significantly increased mitochondrial abnormalities in Swiss mice on the HF diet (P<0.05). In B6 mice, both CTRL and HF oocytes contained high proportions of abnormal mitochondria compared to the CTRL group of the Swiss mice, explaining the lack of HF diet effects in B6 oocyte ultrastructure. We conclude that a HF diet has a significant impact on both metabolic health and oocyte quality. However, the Swiss model seems more sensitive to Western type diet insult, making it more suitable for research focusing on metabolic health and oocyte quality than the B6 strain. HF diet-exposed Swiss mice showed differences (compared to CTRL) in their serum profile. Alterations in mitochondrial activity, structures and oxidative stress were induced by HF diet in the Swiss mice and not the B6, despite that B6 oocytes also showed higher lipid droplet accumulation. Furthermore, even the B6 mice that were fed a normal control diet showed deviant oocyte quality, clearly shown by morphological signs of lower quality and mitochondrial abnormalities.