vasorum, the microvascular network which supplies the cells within the walls of large muscular arteries.

**METHODS/RESULTS:** In this study, we investigated the possible correlation between vasa vasorum disruption and the progression and development of atherosclerosis. We have established a new model of hyperglycemia-induced atherosclerosis in ApoE−/−Ins2+/Akita mice. Aortas, hearts, eyes and pancreas were isolated from 5, 10, 15, 20 and 25 week old normoglycemic and hyperglycemic mice. Retinal and vasa vasorum microvessel density and atherosclerotic lesion areas were quantified in normoglycemic and hyperglycemic mice. The data indicate that atherosclerotic lesion development in normoglycemic ApoE-deficient mice is associated with expansion of the number of microvessels in the vasa vasorum. This likely corresponds to increasing blood supply demands of the thickening artery wall, and is consistent with previous findings. In hyperglycemic ApoE-deficient mice there appears to be no comparable change in the number of microvessels, despite the fact that these lesions are significantly larger. A localized deficiency in VEGF appears to be responsible for this defect. In support of a direct link between micro- and macrovascular disease, supplementation with benfotiamine, an experimental compound used to treat retinopathy, attenuates arterogenesis in hyperglycemic ApoE-deficient mice.

**CONCLUSIONS:** These findings suggest that, in addition to retinal and glomerular capillary beds, hyperglycemia alters the microvessel structure of the vasa vasorum. Such microvascular changes directly correlate to the development and progression of atherosclerosis in hyperglycemic ApoE-deficient mice.

**CDA**

**031**

**A HIGH FAT DIET DOES NOT INDUCE HYPERCHOLESTEROLEMIA IN P53+/− MICE**

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**BACKGROUND:** The tumor suppressor protein p53 is now emerging as a metabolic regulator in glycolysis, fatty acid oxidation and mitochondrial respiration. Recent studies have linked p53 to ageing and oxidative stress. Our objective was to study the role of p53 in the development of hypertension, impaired cholesterol and glucose metabolism in mice challenged with a high fat diet (HFD).

**METHODS:** Three-month old C57Bl/6 (WT) and p53+/− male mice were fed a regular (RD) or a HFD for 3 months. Blood pressure was recorded weakly by a tail-cuff device. Glucose, insulin and lipids were measured in the plasma. Cholesterol levels were also measured in livers and gene expression related to cholesterol metabolism were assessed by quantitative PCR.

**RESULTS:** No changes in systolic blood pressure were observed between groups. Glucose levels tended to increase in both WT and p53+/− mice following the HFD (mmol/L; WT: RD = 14.8±1.4, HFD = 20.5±2.3; p53+/−: RD = 14.4±2.1, HFD = 20.3±3.1; n=7-8; p=0.1), while insulin levels were similar. Interestingly, while plasma total cholesterol levels increased in WT mice, hypercholesterolemia was not observed in p53+/− mice fed a HFD (mmol/L; WT: RD = 2.1±0.2, HFD = 3.1±0.2, p<0.05; p53+/−: RD = 2.3±0.1, HFD = 2.6±0.2; n=7-8). Similarly, following HFD, LDL-cholesterol increased 2-fold in WT mice but not in p53+/− mice (mmol/L; WT: RD = 0.6±0.1, HFD = 1.2±0.1, p<0.05; p53+/−: RD = 0.8±0.1, HFD = 0.8±0.2; n=7-8). In contrast, liver total cholesterol levels were slightly increased in p53+/− mice following the diet (mg/g; WT: RD =12.2±1.4, HFD =14.0±1.3; p53+/−: RD =12.6±1.1, HFD =16.7±1.3, p<0.05; n=7-8). Gene expression of HMG CoA reductase, the enzyme responsible for cholesterol synthesis, and LDL receptor did not change. Gene expression of ABCG5, a cholesterol efflux transporter, increased 2-fold following the HFD in both WT and p53+/− mice (a.u.; WT: RD=1.0±0.2, HFD=2.0±0.2; p53+/−: RD=0.9±0.2, HFD=2.0±0.3; n<0.05, n=5-7). The expression of Cyp7a1, the main enzyme for bile acid synthesis, was higher in p53+/− mice than in WT under the RD, and was up-regulated by the HFD only in WT mice (a.u.; WT: RD=1.0±0.2, HFD=2.1±0.4; p53+/−: RD=2.3±0.3, HFD=2.4±0.7; p<0.05, n=5-7). Finally, the previously demonstrated p53 target gene SHP, which abrogates Cyp7a1 expression, was down-regulated under the RD and the HFD in p53+/− mice (a.u.; WT: RD=1.0±0.1, HFD=1.0±0.1; p53+/−: RD=0.6±0.1, HFD=0.6±0.1; p<0.05, n=6-7).

**CONCLUSION:** While p53 does not regulate glucose homeostasis or blood pressure, our data suggest that p53 could play a role in cholesterol and bile acid metabolism. Higher expression of Cyp7a1, as in in p53+/− mice, could help prevent hypercholesterolemia induced by a HFD.

**CIHR**

**032**

**INVESTIGATING THE ROLE OF THE HEXOSAMINE BIOSYNTHESIS PATHWAY IN DIABETIC ATHEROSCLEROSIS**

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**BACKGROUND:** Diabetes mellitus dramatically increases the risk for atherosclerotic cardiovascular disease. The molecular mechanisms by which this occurs are not known. We have established that chronic hyperglycemia promotes an increase in glucose flux through the hexosamine biosynthesis pathway (HBP). Central to this pathway is glutamine:fructose-6-phosphate amidotransferase (GFAT), the rate-limiting enzyme controlling the conversion of glucose to glucosamine. We have shown that glucosamine is a potent inducer of endoplasmic reticulum (ER) stress, which is characterized by the accumulation of misfolded proteins in the ER. ER stress can initiate a