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EARLY LIFE EXPOSURE TO MATERNAL OBESITY PERTURBS RENAL MORPHOLOGY IN MICE

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Introduction The incidence of Chronic Kidney Disease (CKD) has risen globally by 83% since 1990, concurrently with type 2 diabetes and metabolic syndrome. Studies of maternal under-nutrition during pregnancy have highlighted that the kidney can be adversely "programmed" resulting in fewer filtration units, a factor linked to the pathogenesis of CKD, hypertension and cardiovascular disease (CVD). Despite the dramatic increase in obesity in recent years, the effect of maternal over-nutrition/obesity during pregnancy on offspring kidney structure and function remains largely unexplored. The aim of the current study was to define the effects of maternal over-nutrition on offspring kidney structure using a mouse model of maternal diet-induced obesity.

Methods Female C57BL/6 mice were fed a high fat diet supplemented with sweetened condensed milk for six weeks prior to pregnancy and throughout gestation and lactation. This led to a doubling in maternal body fat. Male offspring were studied at 3 weeks of age. Kidneys were harvested, sectioned and stained with Haematoxylin and Eosin. Nephrons were counted in whole sections at even interspaces throughout the kidney to estimate the number of nephrons within a given area. Glomeruli diameters were also measured as an indicator of glomerular area.

Results There was no difference in absolute kidney weight between the 2 offspring groups (p = 0.95). Offspring exposed to a maternal obesogenic diet had significantly larger combined renal cortex and medulla areas than offspring exposed to a maternal chow diet (17.4 mm² vs 12.5 mm² respectively [p = 0.0136]). However, the number of nephrons/mm² within the cortex and medulla was significantly reduced in offspring of obese pregnancies when compared to controls (2.2/mm² vs. $3.5/\text{mm}^2$ respectively [p = 0.0047]). The mean glomerulus diameter was also significantly larger within offspring of obese pregnancies compared with offspring of control pregnancies (53.7 um vs. 46.3 um respectively [p < 0.0001]).

Conclusions These results suggest that there is compensatory individual glomerular hypertrophy due to a reduced glomeruli density in offspring exposed to maternal obesity during pregnancy and lactation, and that these individuals may therefore be more at risk of developing renal disease and associated CVD in later life. These findings highlight the importance of further studying the long-term consequences of these early morphological changes.



ENRICHMENT OF THROMBIN ACTIVATABLE FIBRINOLYSIS INHIBITOR (TAFI), A NOVEL PRO-THROMBOTIC PROTEIN IN LIPOPROTEINS OF SOUTH ASIAN PATIENTS WITH CORONARY ARTERY DISEASE

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Introduction CAD is a leading cause of mortality in the UK with South Asians at heightened risk, owing to their disproportionately high prevalence of diabetes and metabolic syndrome. Simplistic notion of lipoprotein was transporters of

lipids has been challenged, with a growing appreciation of their functionality, due to their carriage of low abundant proteins which are concerned with redox, inflammation and coagulation. In this study we sought to compare the lipoproteins and their associated protein cargoes between South Asian and Caucasian patients with CAD to further understand the differential risk that exists.

Methods South Asian males (n = 51, age mean \pm SD 58 \pm 8.6years) and Caucasian males (n = 49, age mean \pm SD 64 \pm 8.7years) with angiographic evidence of CAD were recruited, after fulfilling the inclusion criteria, into this single centre prospective cohort study. Blood was withdrawn from the consented patients. Lipoproteins and their associated proteins were isolated using a novel lipoaffinity resin. A bottom-up label-free unbiased lipoproteomic discovery workflow was utilised. Samples were analysed on a Waters G2S high definition ion mobility enabled mass spectrometer. Data analysis was executed using Progenesis Qi with a stringent FDR of 1%.

Results As expected South Asians were younger and had a higher prevalence of diabetes. Renal function, lipid parameters, burden of CAD and cardiovascular medication prescription were equivalent between the two ethnicities. 272 proteins were identified in both groups, of which 28 demonstrated significant differential expression (P < 0.05). South Asians were found to have enrichment of proteins concerned with acute inflammation (alpha-1 acid glycoprotein), complement activation (ficolin-2), extracellular remodelling (thrombospondin-1), endothelial dysfunction (profilin-1) and pro-thrombosis (thrombin activatable fibrinolysis inhibitor [TAFI]/carboxypeptidase B2) relative to Caucasians. South Asians had depletion of tetranectin, concerned with fibrinolysis, compared to their Caucasian counterparts. Biomarker verification revealed that plasma levels of TAFI were significantly higher in South Asian patients compared to Caucasian patients with CAD, using a single site in-house immunoassay (P = 0.045).

Conclusion CAD remodels the lipoproteins and their associated protein cargo with ethnic specific alterations, such that South Asian patients have a predominance of pro-inflammatory and pro-thrombotic proteins compared to Caucasian patients. Higher plasma levels of TAFI in the South Asian patients relative to the Caucasian patients, may contribute to a pro-thrombotic state and to their excess CAD risk.

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LOSS OF ENDOTHELIAL ENDOGLIN LEADS TO HEART FAILURE

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Introduction Endoglin is a co-receptor for members of the transforming growth factor-beta superfamily of ligands, and regulates angiogenesis. Patients carrying mutations in the endoglin gene develop Hereditary Haemorrhagic Telangiectasia (HHT), a disorder characterised by vascular malformations and bleeding. Endoglin is mainly expressed in vascular endothelial cells, is required for normal blood vessel development, but its role in the adult vasculature is not yet understood.

Methods To investigate the role of endoglin in the adult vasculature, we used 12 week old Eng^{fl/fl}; *Cdh5Cre-ER*^{T2} mice to generate endothelial-specific depletion of endoglin (Eng-iKO^e).