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Fasting Pancreatic Polypeptide Predicts Incident Microvascular and Macrovascular Complications of Type 2 Diabetes

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STEP 6: ABSTRACT BODY:

Background: Pancreatic polypeptide (PP) is elevated in people with Type 2 Diabetes (T2D) or with increased visceral adiposity, risk factors for arterial disease. PP acts at neuropeptide Y (NPY) receptors with effects demonstrated on body composition, arterial tone, and retinal vasculature.

Hypothesis: We hypothesised that addition of PP to established factors would enhance estimates of vascular risk in people with T2D. We further hypothesised that PP might have direct effects in glucose sensitive tissues.

Methods: Animal study: Continuous subcutaneous PP infusion for four weeks in a high fat diet mouse model; retinal mRNA obtained using Laser Capture Microdissection and submitted for Ingenuity Pathway analysis. Human study: Fasting PP measured at enrolment in 1478 participants (224 normal glucose tolerance, 224 prediabetes, 1030 T2D) recruited at Imperial College London Diabetes Centre Abu Dhabi; microvascular and microvascular complications of diabetes recorded over median 5.5 (IQR 4.9–5.8) years follow-up.

Results: Animal study: PP infusion was associated with changes in retinal gene expression potentially influencing neuronal survival including BMP receptors, TWEAK and TNFR1, and inhibition of upstream regulators including DAP3 and ALKBH1, even with unaltered weight, BP and blood glucose compared with pair-fed controls. Human study: In univariate analysis and adjusting for established factors including age, diabetes duration, BMI, sBP, smoking and HbA1c, log2(PP) was significantly associated with incident retinopathy (64 events; univariate: hazard ratio (HR) 1.39 (1.14–1.68) p < 0.001), adjusted: HR 1.26 (1.04–1.53) p=0.021), incident albuminuria (34 events; univariate: HR 1.48 (1.14–1.93) p=0.003, adjusted: HR 1.61 (1.21–2.14) p=0.001, and incident macrovascular disease (74 events; univariate: HR 1.46 (1.22–1.74) p<0.0001, adjusted: HR 1.32 (1.09–1.61), p=0.005), in individuals with T2D. Addition of PP to fully adjusted models resulted in modest improvements in the c-statistic (retinopathy: 0.74 without PP, 0.77 with PP; albuminuria: 0.65 without PP, 0.70 with PP; macrovascular: 0.72 without PP, 0.74 with PP). Adjusting for glycaemic status, BMI, sex, age and family history, PP was associated

with increased hazard of progression to T2D in participants not diabetic at enrolment (HR 1.40 (1.08–1.82), p=0.011).

Conclusions: Elevated fasting PP predicts incident vascular complications of diabetes, independent of known risk factors. Tonic elevation of PP in the mouse affects retinal gene expression, influencing pathways which may influence neuronal survival. Our results suggest roles for the PP-fold family of peptides in the pathophysiology of diabetic complications and vascular risk stratification.

Author Disclosure Information:

A.H. Sam: None. **A.J. Buckley:** None. **B.Y. Lam:** None. **P.R. Bech:** None. **K. Meeran:** None. **M.T. Barakat:** None. **S.R. Bloom:** None. **G.S. Yeo:** None. **N.G. Lessan:** None. **K.G. Murphy:** None.

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