ORAL SESSION

ORAL SESSION 5A:
KIDNEY

OP.5A.02 DYSREGULATION OF MICRORNA-181A CAUSED BY OVERACTIVE RENAL SYMPATHETIC NERVES CONTRIBUTES TO ELEVATED RENAL RENIN MRNA AND HYPERTENSION IN SCHLAGER BPH/2J MICE

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Objective: BPH/2J mice are a genetic model of hypertension driven by greater activity of the sympathetic nervous system (SNS) and renin-angiotensin system (RAS). BPH/2J mice display high levels of renal renin mRNA accompanied by low levels of its negative regulator microRNA-181a (miR181a), which is akin to that observed in hypertensive patients. Since miR181a levels also tended to correlate with the depressor response to ganglion blockade, we hypothesise that high renal sympathetic activity reduces miR181a levels, ultimately contributing to the augmented activity of the RAS in BPH/2J mice.

Design and method: To determine whether administering an in vivo miR-181a mimic or renal denervation can increase renal miR-181a abundance to reduce renal renin mRNA, RAS activity and hypertension in BPH/2J mice. Blood pressure (BP) in BPH/2J and normotensive BPN/3J mice was measured via pre-implanted radiotelemetry probes. One group were administered miR-181a mimic or a negative control (25nmol, n = 6–10) using an in vivo kidney specific transfection reagent and BP measured for 24hrs. Another group underwent renal denervation or sham surgery (n = 7–12) and BP measured for 3 weeks. Following these interventions, the BP response to ACE inhibition (enalaprilat) was determined and renal miR181a and renin mRNA abundance measured.

Results: Mir181a levels were greater in denervated BPH-2J mice compared with sham ($P < 0.015$). Furthermore renal renin mRNA abundance was lower in denervated ($P < 0.05$) and mimic treated BPH/2J mice ($P < 0.001$) compared with their respective controls. BP was reduced more after denervation than sham surgery in BPH/2J ($P < 0.001$) but not BPN/3J mice ($P = 0.51$). There was a peak hypotensive effect of the mimic 12–15hrs after injection in BPH/2J mice (-5.3 ± 1.4mmHg, $P < 0.001$) which was not present in negative control treated BPH/2J mice ($P = 0.25$) or in mimic or negative control treated BPN/3J mice ($P > 0.15$). The depressor response to enalaprilat was enhanced in denervated BPH/2J compared with sham ($P < 0.003$), whereas it was abolished in mimic treated BPH/2J mice compared with negative control ($P < 0.001$).

Conclusions: Taken together these findings provide the first in vivo evidence that elevated RSNA reduces miR-181a levels, which can contribute to greater renal renin mRNA level and hypertension in BPH/2J mice.

OP.5A.03 NOVEL STRATEGIES TO IMPROVE THE MANAGEMENT OF ALBUMINURIA IN HYPERTENSIVE DIABETIC PATIENTS

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Objective: After progressing with identification of genomic determinants of diabetic nephropathy, we evaluated the management of microalbuminuria in hypertensive patients with type 2 diabetes (T2D).

Design and method: Clinical Practice in Diabetes Study (NCT01907958) is a multicenter stepped wedge cluster randomized trial of family practice clinics comparing the effect of introducing a Point of Care Testing (POCT) for urine albumin to usual practice in hypertensive patients with T2D and genetic testing in general practice. A total of 8 sites were involved, totaling 244 patients with uncontrolled hypertension followed for a period of 18 months. Sites were randomized to implement POCT sequentially.

Results: At entry, 40% of patients were found to have albuminuria and 72% to have HbA1c > 6.5%. Albumin/creatinine ratio correlated with systolic blood pressure (SBP) ($r = 0.113$, p-value = 0.015) and HbA1c ($r = 0.22$, p-value = 0.001). SBP was not statistically different between microalbuminuric and normoalbuminuric patients (144 mmHg for both, p-value = 0.92) and HbA1c (7.3 for both, p-value = 0.89), suggesting that microalbuminuria cannot be predicted from uncontrolled BP or HbA1c without its direct measurement. Introduction of POCT led to an increase in normoalbuminuric patients over the course of the study (from 55% to 67%) while the percentage of normoalbuminuric patients did not increase in the control group. More patients also reached the target BP of 130/80 mmHg in those exposed to POCT (54%) compared to controls (38%). Among those who had reached the target SBP, 77% were receiving a combination therapy that included an ACEI or an ARB. Gene expression analyses identified 301 differentially expressed genes between patients who progressed from normo- to micro- and from micro- to macro-albuminuria with 132 genes associated to kidney phenotypes.

Conclusions: There is a need for improvement in diagnosis and management of albuminuria in hypertensive T2D patients. Implementation of a POCT for albuminuria increased the number of patients at target BP and normal albuminuria. High BP and HbA1c are poor indicators of kidney damage. Genetic markers that correlate with albuminuria in hypertensive patients with T2D should be considered as future biomarkers for treatment initiation.

OP.5A.04 A URINARY FRAGMENT OF MUCIN 1 SUBUNIT ALPHA IS A NOVEL BIOMARKER PREDICTING RENAL DYSFUNCTION IN THE GENERAL POPULATION

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Objective: Chronic kidney disease (CKD) is a major health problem affecting the quality of life of millions of people. Renal interstitial fibrosis is a universal predictor of the decline in renal function and is characterized by exaggerated deposition of extracellular matrix (ECM) by an expanding population of fibroblasts and myofibroblasts. Our objective was to gain insight in the pathophysiological pathways leading to renal injury by sequencing urinary peptides and thereby identifying the parent proteins from which they are derived. In a representative population sample, we investigated the associations of eGFR with sequenced urinary fragments markers.

Design and method: In 805 randomly recruited Flemish (50.8% women; mean age, 51.1 years), we estimated glomerular filtration rate (eGFR) by the CKD-EPI method. We staged CKD according to the KDOQI guideline. We analysed 74 sequenced urinary peptides with signal amplitude different from undetectable in >95% of participants. Follow-up measurements of eGFR and CKD stage were available in 597 participants.

Results: In multivariable analyses, baseline eGFR decreased ($P <= 0.022$) with urinary fragments of mucin 1 (standardized association size expressed in mL/min/1.73 m^2, −4.48), collagen III (−2.84) and fibrinogen (−1.70) and was bi-directionally associated ($P <= 0.0006$) with two urinary collagen I fragments (+2.28 and −3.20). eGFR changes over 5 years (follow-up minus baseline) resulted in consistent estimates ($P <= 0.025$) for mucin 1 (−1.85), collagen (−1.37 to 1.43) and fibrinogen (-1.45) fragments. Relative risk of having or progressing to CKD stage >= 3 was associated with mucin 1. Partial least square analysis confirmed mucin 1 as the strongest urinary marker associated with decreased eGFR with a score of 2.47 compared with 1.80 for a collagen I fragment as next contender. Mucin 1 predicted progression to CKD stage >= 3 over and beyond microalbuminuria ($P = 0.011$).

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