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Objective: Telmisartan/S-Amlodipine (TEL/S-AML) single-pill combination (SPC) may effectively lower blood pressure (BP) lowering and exhibit renal protective effects, as angiotensin receptor blockers are acknowledged for such benefits. However, there is a scarcity of studies validating these effects in real-world settings. Herein, we assessed the BP-lowering effects and safety, with a specific focus on renal function, after over 6 months of administration in Korean hypertensive patients.

Design and method: This study constitutes a non-interventional, multicenter, retrospective observational investigation that includes individuals diagnosed with essential hypertension and treated with the TEL/S-AML SPC for a period exceeding 6 months. We analyzed the serial changes in BP, serum electrolytes, and creatinine-based estimated glomerular filtration rates (eGFRs). We additionally collected data on serious and other adverse events (AEs) and assessed their relationship to TEL/S-AML SPC.

Results: A total number of 4,934 patients were enrolled in this study. Following the administration of TEL/S-AML SPC, both of systolic and diastolic BPs showed a significant decrease throughout the study period (Ps <0.05). AEs were reported in 352 cases among 282 subjects (5.72%), while serious AEs were reported 74 cases among 62 subjects (1.26%). Serious AEs with a potential relation to TEL/S-AML SPC were reported in 3 subjects (0.06%). No change in eGFR was observed over the study period.

Conclusions: The study findings suggest that the TEL/S-AML SPC is effective in lowering BP and may contribute to the preservation of renal function, showing a low incidence of renal complications after over 6 months of administration in Korean hypertensive patients. These results provide support for the assertion that this agent is well-tolerated.

HYPERTENSIVE NEPHROPATHY: TRANSCRIPTOMICS OF KIDNEY BIOPSIES PREDICTS LONG TERM OUTCOME AND IDENTIFIES THERAPEUTIC TARGETS

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Objective: Hypertensive nephropathy (HN) represents a major cause of chronic kidney disease, but it is incompletely understood why some patients show disease progression. Our project aim is to identify potential markers of disease progression and novel therapeutic targets.

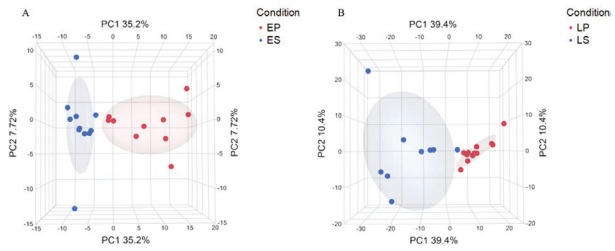
Design and method: Adult patients (n=43; n=16 females, mean age 53 years) with biopsy-verified HN were categorized as 'early' (estimated glomerular filtration rate (eGFR) >45 ml/min/1.73m2) or 'late' disease (eGFR <45 ml/min/1.73m2) at the time of biopsy. Patients were further divided into "stable" (eGFR decline <3 ml/min/year) or "progressive" (eGFR decline >3 ml/min/year or start of renal replacement therapy) after median follow-up of 10 years (5-22). TruSeq Exome sequencing was executed after RNA extraction (miRNeasy FFPE kit, Qiagen) at Novogene, Cambridge, UK. Quality control and data analysis was performed using R Studio (v4.2.0) and QIAGEN Ingenuity Pathway Analysis.

Results: We analyzed the following subgroups of HN patients: early stable (ES, n=11), early progressive (EP, n=11), late stable (LS, n=9) and late progressive (LP, n=12). Differentially expressed genes (DEG, fold change (FC) >1.5 and p-value < 0.05) were identified, with n=265 in ES vs. EP, and n=674 in LS vs. LP.

Principal component analysis (PCA) showed separation of ES vs. EP and LS vs. LP, as depicted in Figure 1A and B. K-nearest neighbour (KNN) analysis of DEG identified a 6-gene classifier in LS vs. LP (19/21 samples correctly classified), while IER5L and CNTNAP5 were the top 2-gene classifier in ES vs. EP (20/21 samples). These classifiers, as well as other DEGs such as PER1, YB1, TIMP3, ADAMTS4, IGFBP5 and EGF could represent novel targets to inhibit disease progression.

Differentially regulated pathways were associated with regulation of TP53 activity and circadian rhythm involving melatonin metabolism in ES vs. EP, and metabolic processes related to water-soluble vitamins, glutathione and sphingolipids in LS vs. LP.

Figure 1: PCA of A) ES *vs.* EP and B) LS *vs.* LP



Conclusions: Transcriptomic profiling from diagnostic kidney biopsies with HN can distinguish future disease progression from non-progression and may identify novel therapeutic targets.

ROLE OF ANGIOTENSIN CONVERTING ENZYME 2 FOR ANGIOTENSIN-(1-7) SIGNALING IN HUMAN PODOCYTES EXPOSED TO FLUID FLOW SHEAR STRESS

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Objective: Glomerular hyperfiltration is linked to increased fluid flow shear stress (FFSS) on podocytes, potentially causing irreversible podocyte impairment and subsequently altering the permeability and integrity of the glomerular filtration barrier. Angiotensin II (AngII) plays a significant role in chronic kidney disease. The adverse effects of AngII are partially countered by alternative signaling pathways in the renin-angiotensin system (RAS), comprising angiotensin-converting enzyme 2 (ACE2), angiotensin-(1-7) (Ang-[1-7]), and the Mas1 receptor (MAS1). This antagonistic pathway might confer renoprotective effects, e.g. by facilitating anti-inflammatory processes. Given the incomplete understanding of the pathomechanisms and signaling pathways triggering podocyte damage due to FFSS, our objective is to elucidate the influence of ACE2 in human podocytes in the context of glomerular hyperfiltration.

Design and method: Gene expression analyses and immunofluorescence staining of ACE2 and MAS1 were conducted on conditionally immortalized human podocytes (hPCs). For mechanistic studies, hPCs were cultured on collagen IV-coated Culture Slips®, placed in a Streamer® Shear Stress Device and subjected to FFSS of 1 dyne/cm^2 for 2 hours. Control cells remained unexposed to FFSS. Subsequently, the rate of spiked AngII conversion to Ang-[1-7] in presence and absence of the specific ACE2 inhibitor MLN-4760 was assessed in whole cell lysates and at the cell surface.

Results: In vitro, hPCs express ACE2 and MAS1 as central elements of the alternative RAS-signaling pathways. RNA-expression levels of ACE2 did not exhibit significant alterations under FFSS compared to the control. FFSS exposure elevated the rate of AngII conversion to Ang-[1-7] in cell lysates compared to control conditions, while the conversion rate at the cell surface remained unaltered. The formation of Ang-[1-7] at the cell surface was diminished by MLN-4760, whereas the inhibitor displayed no significant effect in whole cell lysates.

Conclusions: Our findings show an increased rate of AngII conversion to Ang-[1-7] in hPC lysates following FFSS, which is independent of ACE2. On the cell surface, Ang-[1-7] formation is mediated by ACE2 but remains unchanged under FFSS. These results indicate that ACE2 regulation does not play a central role for Ang-[1-7] formation upon FFSS in human podocytes.

PREDICTORS OF KIDNEY EVENTS IN TYPE 2 DIABETES MELLITUS PATIENTS WITH CHRONIC HEART FAILURE PATIENTS

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Objective: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have a favorable impact on the kidney function in patients with heart failure (HF), while there is no clear evidence of what factors predict this effect. The aim of the study was to identify plausible predictors for kidney function outcome among patients with HF and investigate their association with SGLT2i.

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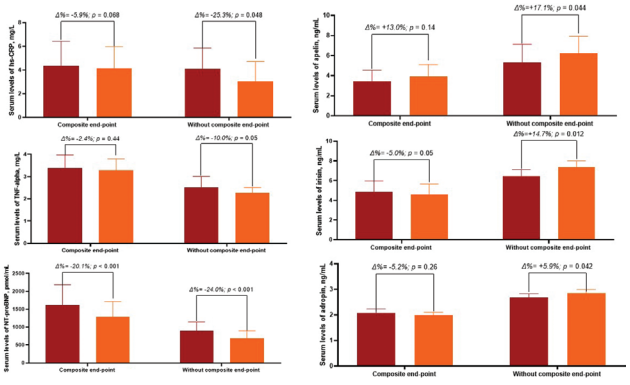

Design and method: We prospectively enrolled 480 patients with type 2 diabetes mellitus (T2DM) treated with diet and metformin and concomitant chronic HF and followed them for 52 weeks. We determined kidney outcome as a composite event that includes >40% reduced estimated glomerular filtration rate from baseline, newly diagnosed end-stage CKD or kidney replacement therapy. The relevant medical information and measurement of the biomarkers were collected at baseline and at the end of the study.

Results: The composite kidney outcome was detected in 88 (18.3%) patients of the entire population. All patients received guideline-recommended optimal therapy, which was adjusted to phenotype/severity of HF, cardiovascular risk and comorbidity profiles, and fasting glycaemia. Levels of irisin, adropin and apelin significantly increased in patients without clinical endpoint, whereas in those with composite endpoint the biomarker levels exhibited a decrease with borderline statistical significance (Figure 1). Multivariate logistic regression revealed that use of SGLT2i (OR=0.92 p=0.048), baseline serum levels of irisin <4.50 ng/ml (OR=1.51, p=0.001) and adropin <2.10 ng/ml (OR=1.15, p=0.001) along with and a <15% increase in the levels of these biomarkers (OR=1.60, p=0.001)and <6% (OR=1.21, p=0.001), respectively, remained an independent predictor for composite kidney endpoint. We established that irisin <4.5 ng/ml and <15% increase in irisin serum levels added more valuable predictive information than the reference variable. However, the combination of irisin <4.5 ng/ml at baseline and <15% increase in irisin serum levels (area under curve = 0.91, 95% confident interval = 0.87-0.95) improved the discriminative value of each biomarker alone.

Conclusions: We suggest that low levels of irisin and its inadequate increase during administration of SGLT2i are promising predictors for unfavorable kidney outcome among patients with T2DM and concomitant HF

PULSE WAVE VELOCITY IS CORRELATED WITH PLASMA CREATININE LEVELS AND GLOMERULAR FILTRATION RATE IN PATIENTS WITH CARDIOVASCULAR RISK FACTORS

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Objective: Scientific evidence suggests that the kidneys' role in hypertension is mostly linked to the association between mean arterial pressure (MAP) and vascular resistance. In recent publications, two key indicators of arterial stiffness, pulse pressure (PP) and pulse wave velocity (PWV) have been found to be important predictors of the cardiovascular risk and decline in glomerular filtration rate (GFR). We aimed to study the relationship between variables of pulse wave analysis and renal function in patients with cardiovascular risk factors.

Design and method: Our cross-sectional, descriptive study included patients referred to the clinic within a National Screening Programme for cardiovascular risk factors. The patients underwent anthropomorphic measurements, office blood pressure measurements, pulse wave analysis using a Mobil-O-Graph and standard blood tests such as lipids, glucose and creatinine.

Results: 76 patients entered the study aged 63±10 years, 53% males, 47% females, mean systolic blood pressure (SBP) of 133.8 mmHg (±18.8), mean diastolic blood pressure (DBP) of 84.1mmHg (±11.5), mean arterial pressure (MAP) of 105.6mmHg (±17.7), mean pulse pressure (PP) of 49.8mmHg (±13.2), mean pulse wave velocity (PWV) of 9.3m/s (±1.5) and mean augmentation index (AI) of 24.7 (±16.2). In linear regression analysis, blood creatinine level was significantly correlated with PWV (r= 0.328, p= 0.004), PP (r= 0.249, p= 0.03), MAP (r= 0.297, p= 0.009), SBP (r= 0.337, p= 0.003) and DBP (r= 0.267, p= 0.02). Glomerular filtration rate (GFR) was significantly negatively correlated with PWV (r= -0.465, p= 0.0001) and SBP (r= -0.227, p= 0.049). Multiple regression analysis revealed significant associations of creatinine with PWV and SBP (multiple correlation coefficient (MCC) = 0.402, p=0.0016) and GFR with PWV after adjusting for SBP (MCC = 0.468, p<0.0001).

Conclusions: Pulse wave velocity can predict blood creatinine and glomerular filtration rate in patients with cardiovascular risk factors.

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