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Tryptophan Metabolites Associate with Subclinical and Incident Cardiovascular Disease in CKD
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Background: Inflammation and oxidative stress contribute to the increased cardiovascular disease (CVD) burden in CKD patients. Altered tryptophan catabolism via the kynurenine pathway associates with CVD, but the ability of these specific metabolites to act as biomarkers of CVD risk in CKD warrants further research.

Methods: We measured tryptophan metabolites using targeted mass spectrometry in moderate to severe CKD patients (n=325; median follow-up 3 years). Vascular calcification at the coronary artery and aorta was measured using a 4-slice LightSpeed QXI and reported as Agatston scores. Incident CVD events included myocardial infarction, coronary revascularization procedures, stroke, transient ischemic attack, new-onset heart failure, sudden cardiac death, and peripheral vascular disease requiring revascularization or amputation. Multiple linear regression and Cox proportional hazard analyses assessed the relationship of tryptophan metabolites to subclinical markers of CVD and CVD events.

Results: We found that lower baseline tryptophan levels predicted increased aortic calcification in a fully adjusted model controlling for demographics, CVD history, traditional risk factors, renal function, CRP, and serum albumin (p<0.006). Higher baseline levels of anthranilic acid and hydroxyanthranilic acid predicted increased coronary calcification and higher total Agatston score, respectively, in the fully adjusted model (p<0.03 in both cases). One unit decrease in serum tryptophan at baseline is associated with a 70% decrease in time to incident CVD event when adjusting for demographics, CVD history, risk factors, and renal function (HR: 0.31, p<0.04). Increased anthranilic acid and quinolinic acid independently reduced time to incident CVD event (HR: 1.88, p=0.02; HR: 1.80, p=0.03 respectively), but were not significant in the fully adjusted model.

Conclusions: Lower tryptophan levels are associated with increased aortic calcification and decreased time to incident CVD events. Higher levels of anthranilic acid, hydroxyanthranilic acid, and quinolinic acid are associated with subclinical CVD. Together, these data demonstrate that catabolism of tryptophan via the kynurenine pathway is associated with subclinical CVD and predicts cardiovascular events in CKD.

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PO1776

Abstract Withdrawn

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High Level of Uromodulin Increases the Risk of Hypertension: A Mendelian Randomization Study
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Background: The association of uromodulin with hypertension was clinically observed, but not proved as a causal relationship. We conducted a two-sample Mendelian randomization (MR) analysis to investigate the causal relation between uromodulin and blood pressure based on the public datasets.

Methods: We selected two SNPs for the uUMOD exposure from the Genome-Wide Association Studies (GWAS) meta-analysis study(N=10884) and sixteen SNPs for the uUMOD exposure. The data demonstrate that catholoid (not published) Six summary level studies based on the UKBiobank and ICBP served as outcomes with the sample of hypertension. We examined the adjusted association of medication escalation, a measure of treatment inertia, with age group among adults with uncontrolled hypertension and determined whether this association is modified by sex. We hypothesized that medication escalation for BP control differs by age group and by sex.

Results: We found that lower baseline tryptophan levels predicted increased aortic calcification in a fully adjusted model controlling for demographics, CVD history, traditional risk factors, renal function, CRP, and serum albumin (p<0.006). Higher baseline levels of anthranilic acid and hydroxyanthranilic acid predicted increased coronary calcification and higher total Agatston score, respectively, in the fully adjusted model (p<0.03 in both cases). One unit decrease in serum tryptophan at baseline is associated with a 70% decrease in time to incident CVD event when adjusting for demographics, CVD history, risk factors, and renal function (HR: 0.31, p<0.04). Increased anthranilic acid and quinolinic acid independently reduced time to incident CVD event (HR: 1.88, p=0.02; HR: 1.80, p=0.03 respectively), but were not significant in the fully adjusted model.

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PO1778

Follistatin Is a Potential Novel Therapeutic Agent for Essential Hypertension
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Background: Follistatin (FST) is an inhibitor of several members of the profibrotic TGFβ superfamily. It is highly effective at neutralizing activities, without activity against TGFβ itself. Activities are known to induce inflammation, oxidative stress and fibrosis, all of which contribute to the vascular dysfunction characteristic of hypertension (HTN). We previously showed that FST inhibits kidney fibrosis, improves kidney function and lowers blood pressure (BP) in a hypertensive chronic kidney disease mouse model. While this is a model of secondary HTN, here we seek to analyze the efficacy of FST in improving BP and vascular structure and function in a model of essential HTN.

Methods: Telemeters were implanted in the abdominal aorta of spontaneously hypertensive rats (SHR), a model of essential HTN, and normotensive control Wistar Kyoto (WKY) rats for wireless BP monitoring. Rats were treated with 0.075mg/kg FST or vehicle IP every other day from 12-20 weeks of age (8 weeks). BP was recorded weekly. First branch mesenteric arteries were harvested for analysis of vascular function using myography, assessed for oxidative stress by DHE, or formalin fixed for IHC.

Results: By the end of the study, FST significantly lowered both systolic and diastolic BP in SHRs (208 +/- 9 over 132 +/- 4 mmHg in control and 189 +/- 2 over 123 +/- 2 mmHg in FST-treated SHRs, P < 0.04 and P < 0.03 respectively). SHR vessels showed increased contractility with the a1 adrenergic agonist phenylephrine, which was attenuated by FST. FST also showed hypotensive effects. SHR vessels contained high levels of TGFβ1 itself. Activins are known to induce inflammation, oxidative stress and fibrosis, all of which contribute to the vascular dysfunction characteristic of hypertension (HTN). We previously showed that FST inhibits kidney fibrosis, improves kidney function and lowers blood pressure (BP) in a hypertensive chronic kidney disease mouse model. While this is a model of secondary HTN, here we seek to analyze the efficacy of FST in improving BP and vascular structure and function in a model of essential HTN.

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Conclusions: FST lowers BP in SHR with established HTN, at least in part by reducing vascular oxidative stress and medial thickening. This manifests as improved vascular function, with decreased hypertersispiration to contractile agents and improved endothelial function. Future work will identify the effects of FST on inflammation, and the role of specific activins in essential HTN.

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PO1779

Age and Sex Disparities in Hypertension Treatment Inertia After Implementation of Target BP
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Background: Blood pressure (BP) control decreases with advancing age among women but not men, but reasons for sex disparities remain uncertain. Our institution enrolled four large outpatient primary care clinics in the Target-BP hypertension improvement program in 2018. This hypertension improvement program included audit and feedback of physician prescribing practices of BP lowering medications. We examined the adjusted association of medication escalation, a measure of treatment inertia, with age group among adults with uncontrolled hypertension and determined whether this association is modified by sex. We hypothesized that medication escalation for BP control differs by age group and by sex.

Methods: Adults age 18 years with uncontrolled hypertension (BP ≥ 140/90 mmHg at last visit) receiving primary care at a clinic enrolled in Target-BP and a 1 primary care visit during 2019 were included. Medication escalation was defined as a change in BP lowering medication class or dose during a visit when hypertension was uncontrolled. Mixed effects models were used to calculate adjusted odds of medication escalation by age group (≥ 65, 66-75, ≥ 76 years) after adjustment for demographics and co-morbidities. Interaction term of sex* age group was then fitted in fully adjusted mixed effects models and was significant (P < 0.001). Adjusted odds of medication escalation were then calculated by sex and by age group and adjusted prevalence of medication escalation by age group and by sex was calculated using marginal effects.

Results: Mean age of 5973 adults with uncontrolled hypertension was 65.2 (SD 6.2) years; 54.7% were women; 64.7% were White, 24.0% were Black and 9.9% were Hispanic ethnicity. Figure (left panel) shows that adjusted prevalence of medication escalation declined with advancing age group among men and women combined. Right panel shows the decline in medication escalation with advancing age group differed by sex until age 76+ years.

Conclusions: Medication escalation for uncontrolled hypertension declines with advancing age and this age associated treatment inertia differs by sex.