Relationship Between Biomarkers of Tubular Injury and Intrarenal Hemodynamic Dysfunction in Youth with Type 1 Diabetes

Melissa J. Johnson, BSc[1]; Kalie L. Tommerdahl, MD[1,2,3]; Carissa Vinovskis, MSc[1]; Sushrut Waikar, MD, MPH[4]; Trenton Reinicke, BSc[1]; Chirag R. Parikh, MD, PhD[5]; Wassim Obeid, PhD[5]; Robert G. Nelson, MD, PhD[6]; Daniel H. van Raalte, MD, PhD[7]; Laura Pyle, PhD[8]; Kristen J. Nadeau, MD, MS[1,3]; Petter Bjornstad, MD[1,3,9]

1. Department of Pediatrics, Section of Pediatric Endocrinology, Children's Hospital Colorado and University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA. 2. Barbara Davis Center for Diabetes, University of Colorado School of Medicine, Aurora, Colorado, USA. 3. Ludeman Center for Women's Health Research, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA. 4. Section of Nephrology, Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts, USA. 5. Division of Nephrology, Johns Hopkins School of Medicine, Baltimore, Maryland, USA. 6. Chronic Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona, USA. 7. Diabetes Center, Department of Internal Medicine, Amsterdam University Medical Centers, location VUMC, Amsterdam, The Netherlands. 8. Department of Biostatistics, Colorado School of Public Health, Aurora, Colorado, USA. 9. Department of Medicine, Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA.

Background

- Diabetic kidney disease (DKD) is a well-established complication of type 1 diabetes (T1D).[1]
- Early DKD is largely clinically silent, yet perturbations of intraglomerular hemodynamic function are often present in youth with T1D.[2]
- Ascertainment of intraglomerular hemodynamic function is arduous; arguing for biomarkers to discover T1D youth at risk for early DKD.
- Tubular injury biomarkers kidney injury marker-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), chitinase 3-like protein-1 (YKL-40), monocyte chemoattractant protein-1 (MCP-1), and copeptin have been proposed as screening tools for DKD.[3-7]
- This study sought to investigate the relationship between intraglomerular hemodynamic function and kidney injury biomarkers in youth with T1D.
- We hypothesized that these biomarkers would strongly associate with measures of intraglomerular hemodynamic dysfunction.

Methods

- **Participants:**
  - 50 adolescents aged 12-21 years with T1D of <10 years duration and an HbA1c of <11% from the CASPER study.
  - 20 youth aged 12-21 years without T1D from the Renal-HEIR study.
- **Data Collection:**
  - Participants with T1D underwent measures of glomerular filtration rate (GFR) and renal plasma flow (RPF) during a hyperglycemic clamp (blood glucoses 170-190 mg/dL).
  - GFR and RPF were quantified by iohexol and *p*-aminohippurate clearance, respectively.
  - Urine albumin-to-creatinine ratio was measured by first morning void.
  - Parameters of intraglomerular hemodynamic function were calculated by Gomez equations.[8]
  - Biomarker concentrations were measured via Meso Scale Discovery Platform (MSD-ECL) electrochemiluminescent assays.
- **Statistical Analysis:**
  - Statistical analyses were performed in SAS version 9.4.

Results

Biomarker of Tubular Injury	T1D (n=50)	Controls (n=20)	*P* value
GFR (mL/min)	189 ± 40	136 ± 22	<0.0001
GFR (mL/min/1.73m^2)	183 ± 26	139 ± 8	<0.0001
RPF (mL/min)	820 ± 125	615 ± 65	<0.0001
RPF (ml/min/1.73m^2)	824 ± 120	634 ± 85	<0.0001
R_A (dyne/s/cm^5)	977 ± 554	2494 ± 518	<0.0001
R_E (dyne/s/cm^5)	2041 ± 362	1173 ± 238	<0.0001
RVR (mm Hg/L/min)	0.07 ± 0.01	0.09 ± 0.01	<0.0001
P_{GLO} (mm Hg)	72.76 ± 8.42	56.31 ± 4.38	<0.0001

Data presented as mean ± standard deviation

Biomarker of Tubular Injury	GFR	RPF	UACR*	P_{GLO}	R_A	R_E	RVR
IL-18*	r: 0.13 p=0.36	r: 0.10 p=0.57	r: 0.01 p=0.96	r: 0.16 p=0.36	r: 0.17 p=0.33	r: 0.12 p=0.48	r: 0.13 p=0.43
YKL-40*	**r: 0.43** **p=0.002**	r: 0.29 p=0.08	**r: 0.33** **p=0.02**	**r: 0.45** **p=0.006**	r: -0.17 p=0.31	**r: 0.36** **p=0.03**	r: -0.02 p=0.91
Copeptin	r: 0.15 p=0.32	r: -0.10 p=0.56	r: -0.02 p=0.91	r: -0.05 p=0.79	r: -0.05 p=0.79	r: 0.06 p=0.71	r: -0.02 p=0.91
NGAL	r: 0.05 p=0.72	r: 0.11 p=0.53	r: -0.09 p=0.55	r: 0.18 p=0.28	r: -0.19 p=0.25	r: 0.08 p=0.65	r: -0.08 p=0.62
MCP-1*	r: -0.13 p=0.38	r: -0.00 p=0.98	r: -0.12 p=0.40	r: 0.01 p=0.95	r: -0.19 p=0.27	r: 0.01 p=0.94	r: -0.10 p=0.57
KIM-1	**r: 0.41** **p=0.003**	**r: 0.34** **p=0.04**	**r: 0.50,** **p=0.0002**	**r: 0.52** **p=0.001**	r: -0.27 p=0.10	r: 0.24 p=0.16	r: -0.08 p=0.63

*Indicates log transformation for normalization. All data are Pearson correlations.

- At baseline, the youth with T1D had greater GFR, RFP, glomerular pressure (P_{GLO}), and efferent arteriole resistance (R_E) than controls.
- The youth with T1D had lower renal vascular resistance (RVR) and afferent arteriole resistance (R_A) than controls.
- KIM-1 and YKL-40 positively associated with GFR, P_{GLO}, and urine albumin-to-creatinine ratio (UACR).
- NGAL, IL-18, copeptin, and MCP-1 did not associate with any parameter of intrarenal hemodynamic function.

Discussion

- Intraglomerular hemodynamic dysfunction in youth with T1D of <10 years duration is strongly associated with tubular injury biomarkers YKL-40 and KIM-1 via GFR, PGLO, and UACR.
- YKL-40 and KIM-1 hold potential as potential biomarkers for identifying and subsequently monitoring early kidney dysfunction in youth with T1D.

Future Directions

- Evaluations of the predictive capacity of YKL-40 and KIM-1 for future decline in kidney function.
- Assessments of YKL-40 and KIM-1 in the setting of nephroprotective agents including sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RA) in youth with T1D.
- Currently ongoing kidney biopsy studies will permit us to examine relationships between these circulating tubular injury biomarkers and intrarenal expression patterns of structural evidence of diabetic kidney injury.

References

1. Bjornstad P, Maahs DM, Jensen T, Lanaspa MA, Johnson RJ, Rewers M, Snell-Bergeon JK (2016) Elevated copeptin is associated with atherosclerosis and diabetic kidney disease in adults with type 1 diabetes. J Diabetes Complications 30:1093-1096
2. Mauer M, Drummond K (2002) The Early Natural History of Nephropathy in Type 1 Diabetes. Diabetes 51:1572.
3. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV (2002) Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int 62:237-244.
4. Llorens F, Thüne K, Tahir W, Kanata E, Diaz-Lucena D, Xanthopoulos K, Kovatsi E, Pleschka C, Garcia-Esparcia P, Schmitz M, Ozbay D, Correia S, Correia Â, Milosevic I, Andréoletti O, Fernández-Borges N, Vorberg IM, Glatzel M, Sklaviadis T, Torres JM, Krasemann S, Sánchez-Valle R, Ferrer I, Zerr I (2017) YKL-40 in the brain and cerebrospinal fluid of neurodegenerative dementias. Mol Neurodegener 12:83.
5. Novick D, Schwartsburd B, Pinkus R, Suissa D, Belzer I, Sthoeger Z, Keane WF, Chvatchko Y, Kim SH, Fantuzzi G, Dinarello CA, Rubinstein M (2001) A novel IL-18BP ELISA shows elevated serum IL-18BP in sepsis and extensive decrease of free IL-18. Cytokine 14:334-342.
6. Jin Y, Cao JN, Wang CX, Feng QT, Ye XH, Xu X, Yang CJ (2017) High serum YKL-40 level positively correlates with coronary artery disease. Biomark Med 11:133-139.
7. Tajfard M, Latiff LA, Rahimi HR, Moohebati M, Hasanzadeh M, Emrani AS, Esmaeily H, Taghipour A, Mirhafez SR, Ferns GA, Mardan-Nik M, Mohammadzadeh E, Avan A, Hanachi P, Ghayour-Mobarhan M (2017) Serum concentrations of MCP-1 and IL-6 in combination predict the presence of coronary artery disease and mortality in subjects undergoing coronary angiography. Mol Cell Biochem 435:37-45
8. Gomez DM (1951) Evaluation of renal resistances, with special reference to changes in essential hypertension. J Clin Invest 30:1143-1155

Acknowledgements

- The authors thank the staff and participants of the CASPER and Renal-HEIR studies for their key contributions.
- This study was funded by the Juvenile Diabetes Research Foundation (JDRF) and the National Institute of Digestive and Diabetes and Kidney Diseases (NIDDK).