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

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BACKGROUND

• Diabetic kidney disease (DKD) is a well-established complication of type 1 diabetes (T1D).
• Early DKD is largely clinically silent, yet perturbations of intraglomerular hemodynamic dysfunction are often present in youth with T1D.
• 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 (KIM)-1, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), chitainase 3-like protein-1 (YKL-40), monocyte chemotactic protein-1 (MCP-1), and copeptin have been proposed as screening tools for DKD.
• 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.

RESULTS

<table>
<thead>
<tr>
<th>Biomarker of Tubular Injury</th>
<th>T1D (n=50)</th>
<th>Controls (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (mL/min)</td>
<td>189 ± 40</td>
<td>136 ± 22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GFR (mL/min 1.73m²/1.73m²)</td>
<td>183 ± 26</td>
<td>139 ± 8</td>
<td>&lt;0.0001</td>
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<tr>
<td>RPF (mL/min)</td>
<td>820 ± 125</td>
<td>615 ± 65</td>
<td>&lt;0.0001</td>
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<tr>
<td>RPF (mL/min 1.73m²/1.73m²)</td>
<td>824 ± 120</td>
<td>634 ± 85</td>
<td>&lt;0.0001</td>
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<tr>
<td>RVR (mL/min 1.73m²/1.73m²)</td>
<td>2.07 ± 0.07</td>
<td>2.36 ± 0.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P_e (mM Hg)</td>
<td>72.7 ± 8.42</td>
<td>56.31 ± 4.38</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

Data presented as mean ± standard deviation

• At baseline, the youth with T1D had greater GFR, RPF, glomerular pressure (P_GLO), and effenter arteriolar resistance (R_e) than controls.
• The youth with T1D had lower renal vascular resistance (RVR) and afferent arteriolar resistance (R_a) than controls.
• KIM-1 and YKL-40 positively associated with GFR, P_GLO, and urine albumin-to-creatinine ratio (AUCR).
• NGAL, IL-18, copeptin, and MCP-1 did not associate with any parameter of intrarenal hemodynamic function.

METHODS

• Participants: 20 youth aged 12-21 years with T1D of <10 years duration and an HbA1c of <11% from the CASPER study.
• Data Collection: Participants with T1D underwent measures of glomerular filtration rate (GFR) and renal plasma flow (RPF) during a hyperglycemic clamp (blood glucose 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 measured by Gomez equations.
• Biomarker concentrations were measured via Meso Scale Discovery Platform (MSD-ECL) electrochemiluminescent assays.

Statistical Analysis:

• Statistical analyses were performed in SAS version 9.4.

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, P_GLO, 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 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


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