Glomerular filtration rate predicts pro-vascular progenitor cell depletion: insights from the IPE-PREVENTION and ORIGINS-RCE studies

E. Bakbak¹, A. Krishnaraj¹, A. Quan¹, D.C. Terenzi², P. Puar³, Y. Pan¹, A. Bakbak⁴, B. Barf⁵, K. Terenzi⁶, O.D. Rotstein⁷, H. Teoh¹, L.A. Leiter⁸, D.L. Bhatt⁹, D.A. Hess¹⁰, S. Verma¹

¹St. Michael's Hospital, Division of Cardiac Surgery, Toronto, Canada
²University College Dublin, School of Medicine, Dublin, Ireland
³University of British Columbia, Faculty of Medicine, Vancouver, Canada
⁴Lakeridge Health Oshawa, Oshawa, Canada
⁵Markham Healthplex, Markham, Canada
⁶Langstaff Medical Clinic, Woodbridge, Canada
⁷St. Michael's Hospital, Division of General Surgery, Toronto, Canada
⁸St. Michael's Hospital, Division of Endocrinology and Metabolism, Toronto, Canada
⁹Mount Sinai Heart, New York, United States of America
¹⁰University of Western Ontario, Robarts Research Institute, London, Canada

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Background: People living with cardiometabolic disease and impaired renal function are at increased risk of experiencing adverse cardiovascular outcomes(1,2). Recent evidence indicates that individuals living with atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes (T2D) exhibit a reduction in circulating vascular regenerative (VR) cells that are essential for maintaining blood vessel homeostasis(3). However, there is limited data on whether VR cell content changes in response to cardiometabolic and kidney disorders.

Purpose: We sought to determine if there is an association between estimated glomerular filtration rate (eGFR) and VR cell content in individuals with ASCVD and/or diabetes. Data were from participants enrolled in the IPE-PREVENTION and ORIGINS-RCE studies.

Methods: IPE-PREVENTION participants had moderately elevated triglycerides (1.5 - 5.65 mmol/L) with established ASCVD and/or T2D. ORIGINS-RCE participants had established ASCVD or T2D and at least one additional cardiovascular risk factor. Circulating mononuclear cells were isolated from peripheral blood and characterized using side scatter properties (SSC) and high aldehyde dehydrogenase activity to quantify pro-angiogenic early myeloid progenitor cells (ALDHhi), and primitive versus lineage-specific cell surface marker co-expression. Participants were stratified according to those with an eGFR < 60 mL/min/1.73m², or ≥ 60 mL/min/1.73m².

Results: Median [IQR] eGFR of the pooled cohort (n=169) was 75 [59, 88] mL/min/1.73m²; 45% had an eGFR that was <60 mL/min/1.73m². The stratum with eGFR <60 mL/min/1.73m² had fewer circulating ALDHhiSSClow progenitor cells (0.037 vs. 0.051%; P <0.01) (Figure 1A) and ALDHhiSSClow cells expressing CD34+ and CD133+ (49 vs. 54%; P =0.03) (Figure 1B) than that with an eGFR ≥60 mL/min/1.73m². The predictive value of eGFR on ALDHhiSSClowCD34+CD133+ frequency was conserved even after controlling for age, sex, LDL-C, BMI, and HbA1c (P <0.01) (Table 1). The frequency of ALDHhiSSCmid monocyte precursor cells did not differ based on eGFR status.

Conclusions: Low eGFR was predictive for the depletion of ALDHhiSSClow primitive progenitor cells that co-express the stem cell markers CD133 and CD34 in individuals with ASCVD and/or T2D suggesting that diminished kidney function is associated with a decrease in vessel reparative pro-angiogenic progenitor cell content. Strategies that improve circulating VR cell content in individuals living with kidney and cardiometabolic disease may provide clinically meaningful benefits.

Figure 1

[Diagram showing frequency of ALDHhiSSClow and CD34+CD133+ cells based on eGFR]
<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates</th>
<th>Coefficient</th>
<th>[eGFR] Standard Error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>sex, age, HbA1c</td>
<td>0.165</td>
<td>0.063</td>
<td>0.01</td>
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<tr>
<td>Model 3</td>
<td>sex, age, BMI, and HbA1c</td>
<td>0.181</td>
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<tr>
<td>Model 4</td>
<td>sex, age, BMI, HbA1c, and LDL-C</td>
<td>0.178</td>
<td>0.063</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Table 1