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

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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
<table>
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<tr>
<th>Model</th>
<th>Covariates</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>P value</th>
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<tr>
<td>Model 1</td>
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<td>Model 4</td>
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