Renal progenitor cells an early non-invasive biomarker of silent kidney injury in Fabry disease

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Background and Aims: Fabry's disease (FD), a hereditary condition, is linked to the X chromosome due to a mutation in the gene encoding alpha-galactosidase A (alpha-GalA). This mutation results in a defect in the metabolism of glycosphingolipids, leading to the deposition of globotriaosylceramide (GB3) primarily in organs such as the heart, kidneys, and nervous system.

Renal injury can affect any level of the structure, with the podocytes being the most commonly affected due to their low regeneration and high contact with GB3. This leads to proteinuria, and if it exceeds 0.5 g, it is associated with a rapid deterioration of renal function.

Renal assessment is carried out through blood analysis, proteinuria measurement, ultrasound, and the gold standard, renal biopsy. However, there is a growing trend towards less invasive biomarkers such as lysoGB3 titration in blood and urine, podocyturia, or renal progenitor cells (RPCs) in renal biopsy material or cell culture.

RPCs possess self-renewal, clonogenicity, and multidifferentiation properties, contributing to cellular remodeling. They express specific markers like CD133/CD24 and CD106 in the parietal epithelium of Bowman's capsule. It is known that GB3 expresses CD77.

The proliferative response of RPCs can become dysregulated, leading to detachment and elimination in the urine.

The aim of the study was to demonstrate the presence of renal progenitor cells (RPCs) in urine as a non-invasive early marker for detecting renal damage in patients with Fabry's disease (FD) and to establish a correlation between RPC presence, GB3 deposition, and their potential association with the degree of renal injury.

Method: It is an open observational, case-control, single-center study on the urine of patients with Fabry's disease (FD) considered as cases, patients without a history considered as healthy controls, and patients with non-FD renal disease such as Gittelman syndrome or another biopsy-proven cause as positive controls. Renal progenitor cells (RPCs) were isolated using specific markers and flow cytometry, correlating these findings with renal function and albuminuria.

Results: A total of 75 recent urine samples were processed, corresponding to 59 patients: 16 with Fabry's disease (FD), 11 with Gittelman syndrome, 10 with chronic kidney disease (CKD), and 22 healthy controls. The samples were divided for sediment and microalbuminuria analysis, and separately for the isolation of renal progenitor cells (RPCs). The classification and quantification of the isolated cell types were performed, establishing positivity points using compensation panels with CD3 lymphocyte markers. This was followed by the identification of RPCs through positivity for CD133+/CD24+, CD106+, and CD106– markers. Once RPCs were identified, GB3 marking was carried out using CD77+. Differences were observed among the analyzed patient groups. In healthy controls, there was minimal or no presence of renal progenitor cells (RPCs), except in two patients where isolation was repeated in three different samples, maintaining positivity. Subsequent diagnoses revealed bilateral lithiasis and previously unknown hypertension in these cases. Patients with Gittelman syndrome showed a higher quantity of RPCs compared to healthy controls, but with $P > .05$. However, clear RPCs positivity was evident in patients with Fabry's disease (FD) and chronic kidney disease (CKD) confirmed by biopsy, with $P < .05$. Additionally, differences in the number of RPCs were noted based on the degree of renal disease when correlated with the presence of proteinuria < 0.5 g and > 0.5 g, with $P < .05$.

Conclusion: With these results, we can conclude that renal progenitor cells (RPCs) may serve as an early biomarker for silent renal injury of various etiologies. Furthermore, if we perform labeling with CD77, we can attribute it to the deposition of GB3 in Fabry's disease (FD).

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The proliferative response of renal progenitor cells (RPCs) can become dysregulated, leading to detachment and elimination in the urine. The focus of the study was to look at the presence of RPCs in urine as a non-invasive early marker for detecting renal damage in patients with Fabry's disease (FD). This is correlated between RPC and proteinuria. RPCs with a positive marker for GB3 can define the origin of kidney damage due to FD.

Methods

Observational, case-control, single-center

59 patients

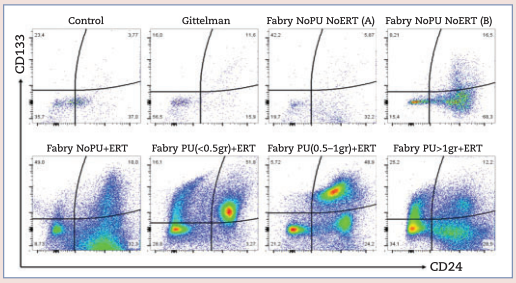
75 urine samples:

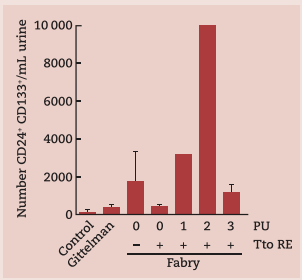
Sediment and microalbuminuria
- Proteinuria < 0.5 or > 0.5 gr

Isolation RPCs
- Positive points CD3 lymphocyte markers
- $CD133^{+}/CD24^{+}$, $CD106^{+/-}$ markers
- GB3 marking $CD77^{+}$

Results

59 patients:
- 22 healthy controls
- 21 positive controls without FD (11 Gittelman, 10 other causes of CKD)
- 16 with FD





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RPCs may serve as an early biomarker for silent renal injury of various etiologies. With CD77, we can attribute it to the deposition of GB3 in Fabry's disease.