Kidney Diseases

Research Article

Kidney Dis 2025;11:332–341
DOI: 10.1159/000545604

Received: December 9, 2024
Accepted: March 10, 2025
Published online: April 14, 2025

Urinary Myeloid Bodies as a Biomarker for Early Diagnosis and Monitoring of Enzyme Replacement Therapy in Fabry Disease

Junlan Yang[a, b] Zhiyuan Wei[a, b] Haifeng Ni[a] Qianqian Wu[a, b] Siqi Peng[a, b] Wen Shi[a, b] Xiaoxu Wang[a, b] Yan Yang[a] Jianan Jiang[b] Jingyuan Cao[c] Yao Wang[d] Liyuan Zhang[e] Aihua Zhang[f] Xiaoliang Zhang[a] Bin Wang[a]

[a]Department of Nephrology, Zhong Da Hospital, Southeast University, Nanjing, China; [b]Southeast University School of Medicine, Nanjing, China; [c]Department of Nephrology, The Affiliated Taizhou People's Hospital of Nanjing Medical University, Taizhou School of Clinical Medicine, Nanjing Medical University, Taizhou, China; [d]Department of Nephrology, Yangzhou First People's Hospital, The Affiliated Hospital of Yangzhou University, Yangzhou, China; [e]Department of Nephrology, Lianyungang First People's Hospital, Lianyungang, China; [f]Department of Nephrology, Children's Hospital of Nanjing Medical University, Nanjing, China

Keywords
Fabry disease · Hereditary disease · Urinary myeloid bodies

Abstract

Introduction: The prevalence of urinary myeloid bodies in Fabry disease patients and their correlation with renal involvement remains unclear. ***Methods:*** This single-center, retrospective study included 25 patients with Fabry disease and 27 controls. We analyzed 24-h urine samples for the presence of urinary myeloid bodies and evaluated clinical data, including serum creatinine, estimated glomerular filtration rate (eGFR), 24-h urinary protein levels, α-Gal A, and Lyso-GL-3. Seven Fabry patients underwent analysis of urine samples before and after 1 year of enzyme replacement therapy (ERT). ***Results:*** Urinary myeloid bodies were detected in 84% of Fabry patients (21 out of 25), with no significant gender differences. None of the healthy controls or patients with other renal disease patients had urinary myeloid bodies. Among the Fabry patients with myeloid bodies, 48% had no proteinuria, and 52% were in CKD1 stage G1. Furthermore, urinary myeloid bodies were detected in 4 patients under the age of 20, despite the absence of or only minimal proteinuria, and these patients all exhibited a substantial number of myeloid bodies. After 1 year of ERT, significant reductions in both the count ($p = 0.043$) and area ratio ($p = 0.028$) of myeloid bodies were observed. ***Conclusion:*** Urinary myeloid bodies are specific to Fabry disease and are associated with early renal injury, even in the absence of proteinuria. These findings suggest that urinary myeloid bodies may serve as a noninvasive biomarker for the early diagnosis of Fabry disease and for monitoring the efficacy of ERT.

Introduction

Fabry disease is a rare X-linked genetic disorder caused by mutations in the GLA gene, leading to reduced or absent α-galactosidase A (α-Gal A) activity and

Junlan Yang, Zhiyuan Wei, and Haifeng Ni contributed equally to this work.

karger@karger.com
www.karger.com/kdd

Correspondence to:
Bin Wang, wangbinhewei@126.com
Xiaoliang Zhang, tonyxlz@163.com
Aihua Zhang, zhaihua@njmu.edu.cn

subsequent lysosomal dysfunction [1]. This results in the pathological accumulation of lipid substances, including globotriaosylceramide (GL-3) and its derivative globotriaosylsphingosine (Lyso-GL-3), in various organs, such as the kidneys, heart, nervous system, and skin, ultimately causing organ dysfunction [2–4]. The clinical phenotype of Fabry disease demonstrates significant heterogeneity [5], with classification into classic and late-onset forms based on the age at onset, clinical manifestations, and the degree of enzyme activity reduction [6]. In the classic form, patients typically exhibit severely reduced or absent residual α-Gal A activity, which is associated with a poorer prognosis. Early signs and symptoms generally manifest during childhood and include neuropathic pain, corneal verticillata, gastrointestinal disturbances, hypohidrosis, and angiokeratomas. Over time, these patients may develop progressive complications such as renal failure, hypertrophic cardiomyopathy, arrhythmias, hearing loss, and stroke.

Renal involvement is a major contributor to disability and mortality in Fabry disease. Early identification of high-risk individuals and timely initiation of targeted therapy are therefore critical for improving patient outcomes [7]. The most common renal manifestations of Fabry disease are proteinuria and renal dysfunction [8], which are widely recognized as markers of kidney injury and indicators for initiating targeted treatment. Studies have demonstrated that enzyme replacement therapy (ERT) is often insufficient to reverse podocyte damage or halt further decline in renal function in patients with proteinuria exceeding 1 g/day [9]. Consequently, it is imperative to identify novel biomarkers of early Fabry-related kidney injury to facilitate earlier initiation of ERT and improve renal prognosis in affected patients [10]. A hallmark histopathological feature of Fabry disease is the presence of multilamellar myelin figures, or "myeloid bodies," which are observable under electron microscopy. These myeloid bodies are critical for diagnosing Fabry disease and are closely associated with disease progression [11, 12]. First identified in the urine sediment of Fabry patients by Katz and Lyons in [13] 1977, their diagnostic value was later substantiated by Murayama's team [14] in 2018. Despite these findings, the prevalence of urinary myeloid bodies and their correlation with Fabry disease progression remain inadequately understood. This study aimed to quantitatively analyze the number and area ratio of myeloid bodies in the urine sediment of patients with Fabry disease, report their prevalence, explore their association with disease progression, and evaluate their potential as a noninvasive biomarker for monitoring the effectiveness of ERT.

Methods

Study Design and Population

This single-center, retrospective study was conducted at the Department of Nephrology, Zhong Da Hospital, Southeast University, between February 2023 and December 2024. Fabry patients included in the study met the following criteria: diagnosis of Fabry disease confirmed by reduced plasma α-Gal A enzyme activity and the presence of GLA gene mutations, with no restriction on age or gender. For comparative purposes, we included 2 healthy individuals with no prior medical conditions, as well as 25 patients with other renal diseases (4 hypertensive nephropathy, 4 diabetic nephropathy, 3 minimal change disease, 3 membranous nephropathy, 3 focal segmental glomerulosclerosis, 3 IgA nephropathy, 3 ANCA-associated glomerulonephritis, and 2 lupus nephritis) who were similar in gender and age for 24-h urine sample collection. Patients were excluded if baseline data were unavailable or if they were unable to provide a 24-h urine sample (minimum 500 mL).

Baseline clinical data, including demographic information (age, gender), clinical manifestations, serum creatinine, estimated glomerular filtration rate (eGFR), and 24-h urinary protein, were collected. In addition, 24-h urine samples were obtained for the preparation of urinary sediment pathological slides. To assess changes in urinary myeloid body excretion pre- and post-treatment, 7 Fabry patients provided 24-h urine samples after completing 1 year of ERT.

Preparation of Urine Sediment Pathological Sections

A 24-h urine sample (minimum 500 mL) was collected from each patient (shown in Fig. 1). The sample was aliquoted into 15 mL centrifuge tubes and centrifuged at 2,500 rpm for 10 min at 4°C. The supernatant was discarded, and the precipitate was retained. This centrifugation process was repeated until all urine samples were processed, resulting in the collection of urine sediment. The sediment was then fixed in 2.5% glutaraldehyde for 4 h, followed by three washes with 0.1 mL of PBS. Afterward, the sediment was fixed with 1% osmium tetroxide for 2 h, rinsed three times with distilled water, and subjected to a graded dehydration protocol. Finally, the sample was embedded, sectioned, and stained to create pathological specimens.

Qualitative and Quantitative Analysis of Urinary Myeloid Bodies

Urine sediment pathological sections were examined using a transmission electron microscope at ×2,500 magnification. Twenty random images per patient were

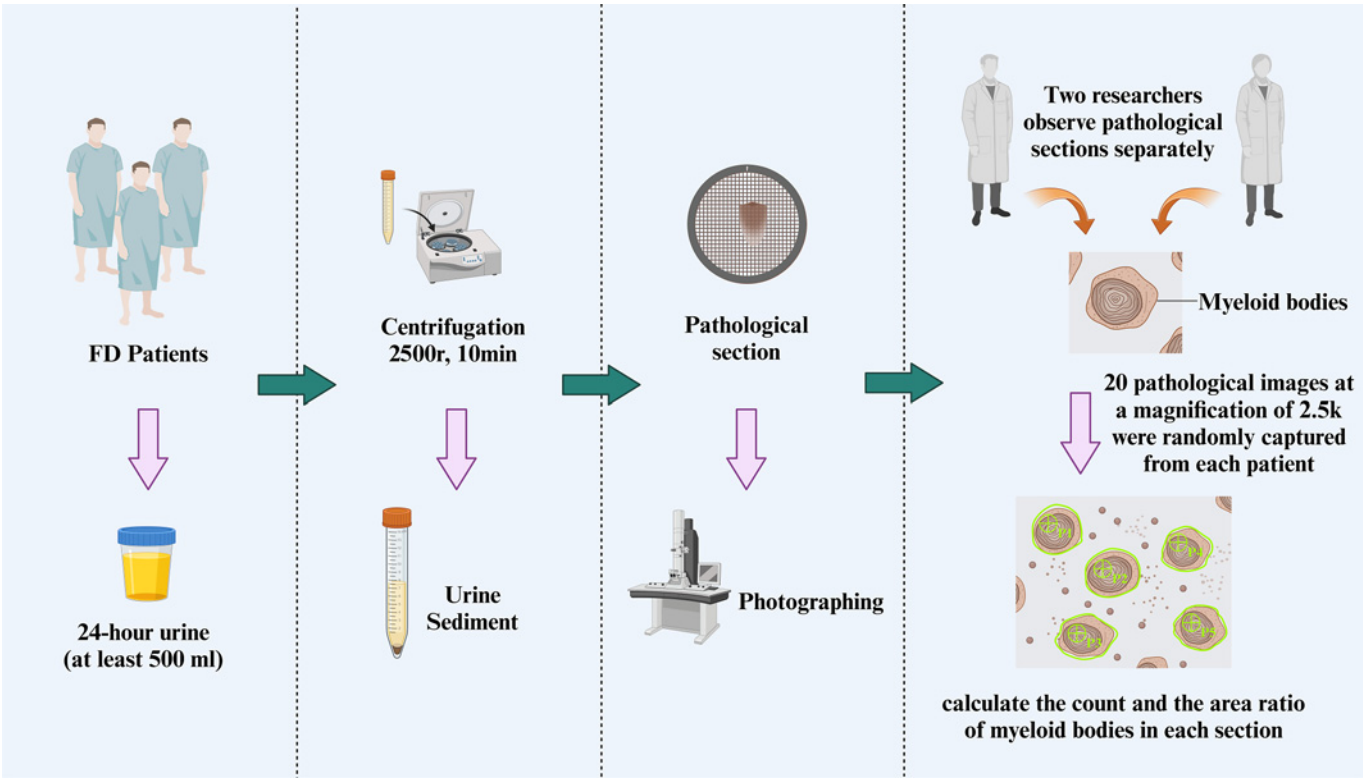

Fig. 1. Quantitative analysis of urinary myeloid bodies.

captured. These images were independently assessed by two researchers who were blinded to each other's findings. Using Image-Pro Plus software, the number of myeloid bodies in each image was counted, the area occupied by these myeloid bodies was outlined, and the ratio of this area to the total field of view area was calculated to determine the myeloid bodies area ratio.

Statistical Analyses

Descriptive statistics were reported as proportions, means with standard deviations, or medians with interquartile ranges as appropriate. Between-group differences and the impact of ERT on urinary myeloid body excretion were analyzed using the Wilcoxon rank-sum test.

Results

Distribution of Urinary Myeloid Bodies in Fabry Patients

This study included 25 Fabry patients (Table 1) and 27 control subjects (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000545604). The median age of the Fabry patient cohort was 43 years, with a male-to-female ratio of 44%–56%. None of the Fabry patients had a history of cationic amphiphilic drug use. Urinary myeloid bodies were detected in 21 patients (84%) (shown in Fig. 2). Comparison between Fabry patients with and without urinary myeloid bodies revealed no statistically significant differences in age, gender, serum creatinine, eGFR, 24-h urinary protein, α-Gal A, or Lyso-GL-3 (Table 2). Although no statistically significant differences were observed, patients with myeloid bodies tended to be younger at diagnosis, had higher serum creatinine levels, and exhibited more proteinuria compared to those without myeloid bodies, suggesting a potentially more severe clinical phenotype. In the control group, 27 individuals were included, consisting of 2 healthy subjects with no prior medical history, from whom no urinary sediment was obtained following centrifugation of 24-h urine samples. The remaining 25 patients with other renal diseases (including 2 patients with lupus nephritis treated with hydroxychloroquine), matched in age and gender with the Fabry disease group, exhibited no urinary myeloid bodies in their urine sediment.

Table 1. Baseline and diagnostic data of 25 Fabry patients

Number	Age, years	Gender	Variant cDNA	α-Gal A, μmol/L/h	Lyso-GL-3, ng/mL	Serum creatinine, μmol/L	CKD stage	eGFR, mL/min/1.73 m^2	Proteinuria	24-h proteinuria, g	Count of myeloid bodies	Area ratio of myeloid bodies	History of cationic amphiphilic drugs
1	38	M	c.902G>A	0.32	18.87	64	1	99.65	0	0.042	0	0	N/A
2	43	M	c.263A>G	0.27	30.79	111	2	72.1	3+	2.325	0	0	N/A
3	57	F	c.641C>A	2.44	6.36	60	1	97.16	0	0.1	0	0	N/A
4	49	F	c.548-1G>T	1.93	5.4	57	1	104.52	1+	0.38	0	0	N/A
5	55	F	c.735G>A	1.4	6.3	97	3	57.3	1+	0.62	8	3.11	N/A
6	42	F	c.974G>A	3.17	4.56	55	1	109.93	0	0.045	0.75	0.13	N/A
7	31	M	c.658C>T	0.64	73.92	873	5	6.32	1+	0.135	0.9	0.18	N/A
8	72	F	c.902G>A	1.44	4.82	56	2	89.45	0	0.18	2.5	0.4	N/A
9	55	M	c.595G>A	0.43	–	61	1	116.9	2+	1.148	1.05	0.4	N/A
10	54	F	c.902G>A	3.09	1.05	110	3	46.78	2+	4.068	0.7	0.49	N/A
11	10	F	c.548-1G>T	4.77	3.45	50	1	110.99	0	–	5	0.91	N/A
12	52	M	c.735G>A	0.32	88.23	72	1	103.28	0	0.046	5.5	0.98	N/A
13	44	F	c.227T>A	3.56	11.84	69	1	92.79	0	0.06	2.45	1.15	N/A
14	10	F	c.548-1G>T	2.91	4.53	66	2	84.08	0	–	9.8	2.13	N/A
15	47	F	c.735G>A	1.88	7.02	56	1	107	0	0.048	3.9	1.49	N/A
16	48	F	c.735G>A	1.33	7.39	68	1	91.19	0	0.286	6.1	1.6	N/A
17	56	F	c.902G>A	4.44	3.9	40	1	111.42	1+	0.189	7.7	1.73	N/A
18	56	F	c.735G>A	3.12	13.68	62	1	97.14	1+	0.304	6.75	2.09	N/A
19	28	M	c.735G>A	0.36	71.09	98	2	87.55	3+	2.66	18.67	5.68	N/A
20	32	M	c.91C>A	0.4	86.29	81	2	77.67	3+	1.393	8.45	2.15	N/A
21	41	F	c.605G>A	1.02	3.97	54	1	114.55	2+	2.736	7.4	2.95	N/A
22	17	M	c.974G>A	0.31	32.5	116	2	78.86	0	0.247	13.05	3.78	N/A
23	19	M	c.227T>A	0.48	72.58	69	1	146.76	0	0.133	7.6	3.95	N/A
24	32	M	c.641C>A	0.85	54.99	86	2	65.89	2+	1.505	10.3	4.98	N/A
25	32	M	c.91C>A	0.4	14.92	92	2	80.95	3+	3.64	27.2	5.25	N/A

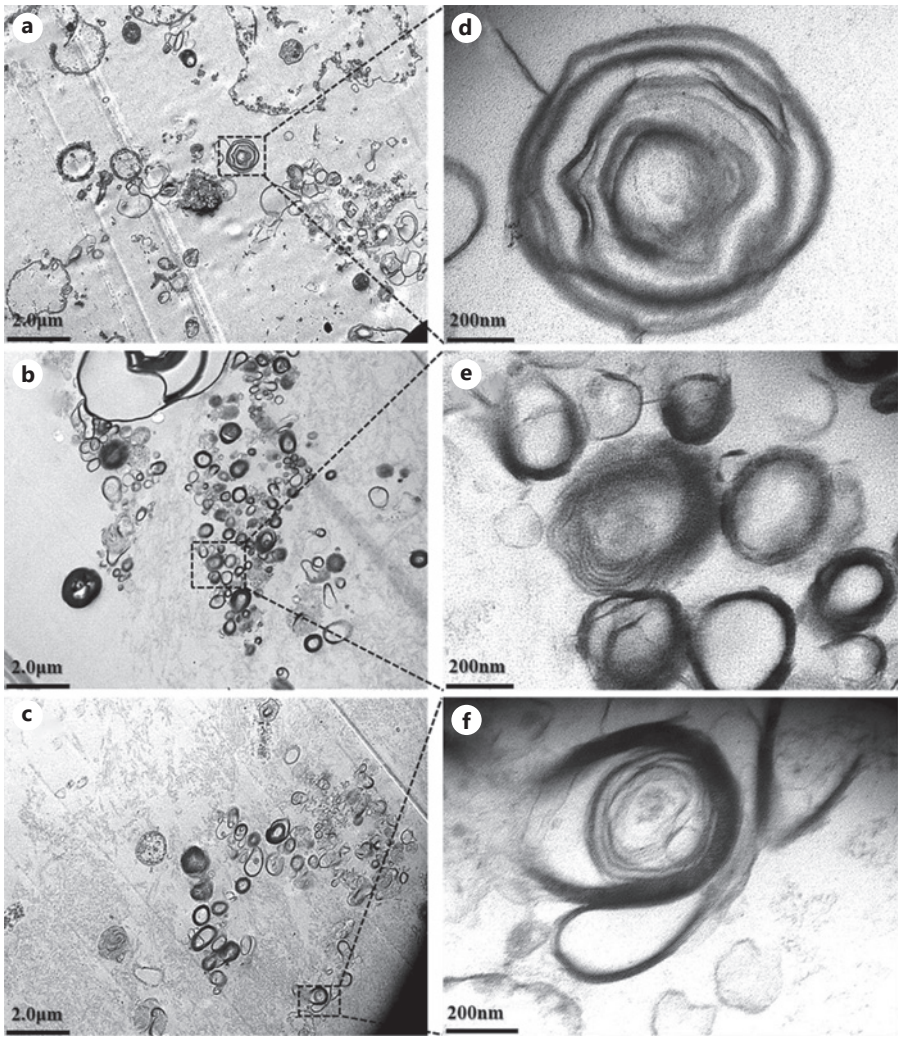

Fig. 2. Typical morphology of urine myeloid bodies in Fabry patients under transmission electron microscopy. **a–c** Transmission electron microscopy images showing typical structures of urinary myeloid bodies (scale bar, 2.0 μm). **d–f** Higher magnification images revealing the multilamellar concentric myelin-like structures of urinary myeloid bodies (scale bar, 200 nm).

Intragroup Analysis of Fabry Patients

Based on the presence of urinary myeloid bodies and proteinuria (defined as urinary protein excretion greater than 0.15 g/24 h or a positive urinary protein test), patients were divided into four groups (shown in Fig. 3). Two patients exhibited neither proteinuria nor myeloid bodies, and their renal function showed no significant abnormalities, while 14 patients presented with both. Seven additional patients showed urinary myeloid body excretion despite the absence of proteinuria. Among these, 4 patients were under the age of 20 (No. 11, No. 14, No. 22, and No. 23). Except for patient No. 22, who had minimal proteinuria, the others did not exhibit proteinuria but showed a significant presence of urinary myeloid bodies. Notably, a pair of twins (No. 11 and No. 14) exhibited normal enzymatic activity levels yet displayed substrate accumulation and urinary myeloid body presence. In one of the twins with lower enzyme activity (No. 14), there was a pronounced Lyso-GL-3 accumulation, a higher urinary myeloid bodies count, and a greater urinary myeloid bodies area ratio. These findings suggest that urinary myeloid body excretion may precede the onset of proteinuria and a decline in enzymatic activity. Only 2 patients (No. 2 and No. 4) exhibited proteinuria in the absence of urinary myeloid bodies. At the time of urinary sediment analysis, they had already received 31 and 32 ERT sessions, respectively. The absence of myeloid body excretion may have been influenced by prior ERT treatment.

An intragroup analysis was conducted on patients with urinary myeloid bodies (shown in Fig. 4). Among these patients, females slightly outnumbered males (12 vs. 9). Four patients were under 20 years old, 5 were between 20 and 39 years, 11 were between 40 and 59 years, and 1 patient was over 59 years. Nearly half of the patients were proteinuria negative; 4 patients had proteinuria 1+ (protein levels between 0.2 g and 1.0 g/L); 4 patients had proteinuria 2+ (1.0 g–2.0 g/L); and 3

Table 2. Clinical characteristics of patients included in this study

Characteristic	Fabry patients				Control (healthy people excluded)	
	total	myeloid body positive	myeloid body negative	*p* value[1]	total	*p* value[2]
N	25	21	4	–	25	–
Male/female	11/14	9/12	2/2	>0.99	14/11	0.57
Age, median (IQR), years	43 (32–54)	42 (31–54)	46 (42–51)	0.37	41 (37–46)	0.63
Serum creatinine, median (IQR), μmol/L	68 (57–92)	69 (56–92)	62 (59–76)	0.82	110 (71–138)	0.01
eGFR, mean±SD, mL/min/1.73 m^2	90.01±26.81	89.37±28.69	93.36±12.56	0.88	67.67±38.68	0.06
Proteinuria positive, *n* (%)	16 (64)	14 (67)	2 (50)	0.60	23 (92)	<0.01
24-h proteinuria, mean±SD, g	0.97±1.27	1.02±1.27	0.71±0.94	0.52	4.05±5.33	0.04
α-Gal A, median (IQR), μmol/L/h	1.33 (0.40–2.91)	1.33 (0.43–3.09)	1.13 (0.31–2.06)	0.35	–	–
Lyso-GL-3, median (IQR), ng/mL	9.62 (4.76–38.12)	9.62 (4.55–59.02)	12.62 (6.12–21.85)	0.94	–	–

IQR, interquartile range; SD, standard deviation. [1]Comparison of patients with and without myeloid bodies in Fabry disease. [2]Comparison between Fabry patients and control (healthy people excluded).

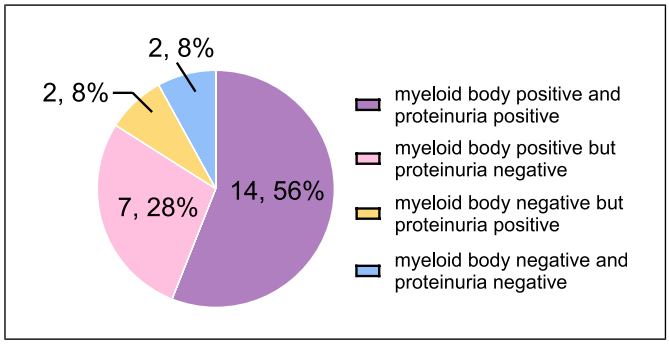

Fig. 3. Sector diagram of urinary myeloid bodies and proteinuria in Fabry patients.

patients had proteinuria 3+ (2.0 g–4.0 g/L). Based on disease duration and eGFR, patients were staged for chronic kidney disease (CKD), over half of the patients were in CKD G1, seven were in CKD G2, two in CKD G3, and one in CKD G5.

Relationship between Urinary Myeloid Body Excretion and the Duration of ERT

In this study, 7 patients completed a 1-year course of ERT, after which their urinary myeloid body count, area ratio, and proteinuria were evaluated (online suppl. Table S2). The results revealed a statistically significant decrease in both the count ($p = 0.043$) and area ratios ($p = 0.028$) of urinary myeloid bodies compared to pre-treatment levels (shown in Fig. 5). Notably, only 1 patient (No. 6) showed a slight increase in urinary myeloid bodies count (an increase from 0.75 to 1.3) and area ratio (an increase from 0.13 to 0.47) after 1-year ERT. Regarding proteinuria, the qualitative proteinuria level of 1 patient (No. 19) decreased from 3+ to 1+, while the remaining patients exhibited no trend of worsening qualitative proteinuria, suggesting that ERT may delay or control disease progression.

Discussion

This study is the first to perform both qualitative and quantitative analyses of urinary myeloid bodies in Fabry patients, yielding several new insights. Myeloid bodies were detected in the urinary sediment of 84% of Fabry patients. Notably, their presence was observed before the onset of proteinuria and renal function decline, indicating their potential utility for early diagnosis. Additionally, after 1 year of ERT, both the number and area ratio of urinary myeloid bodies decreased, highlighting their potential as biomarkers for monitoring ERT effectiveness.

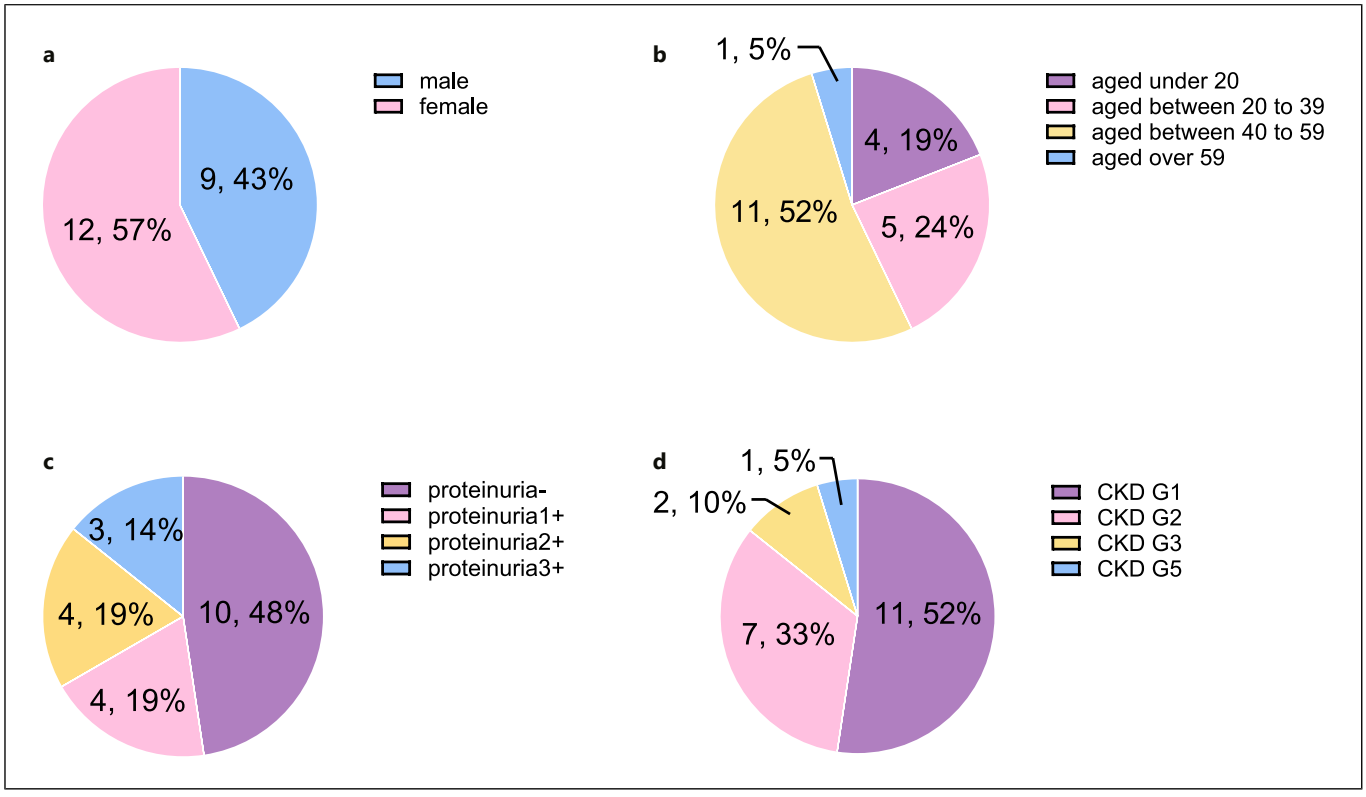

Fig. 4. Internal subgroup analysis of patients with urinary myeloid bodies. **a** Gender distribution. **b** Age distribution. **c** Proteinuria status distribution. **d** Distribution across stages of chronic kidney disease (CKD).

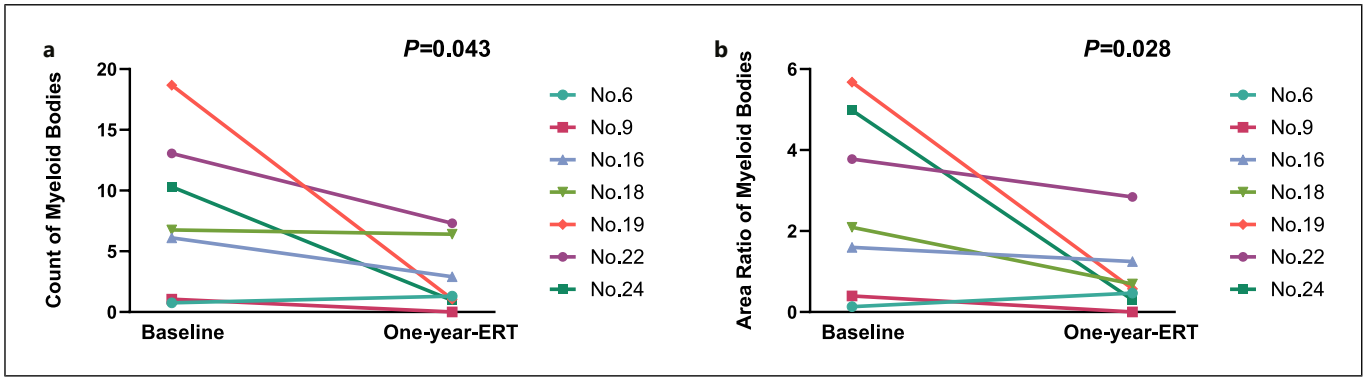

Fig. 5. Quantitative changes in urinary myeloid bodies in Fabry patients after 1 year of ERT, showing alterations in number (**a**) and area ratio (**b**).

Fabry disease affects multiple organs and exhibits highly heterogeneous clinical manifestations, leading to frequent misdiagnosis or missed diagnosis [15, 16]. In patients with Fabry nephropathy [9], reduced α-Gal A activity leads to the accumulation of lipid substrates in podocytes [17, 18], resulting in dysfunction and detachment, which progress to proteinuria and renal insufficiency [19]. Genetic testing is the gold standard for diagnosing Fabry disease; however, it is costly and unsuitable for monitoring therapeutic efficacy. Decreased α-Gal A activity serves as a diagnostic marker in male patients, but due to the random inactivation of the X-chromosome, α-Gal A activity in female

patients may fall within the normal range, leading to misdiagnosis [20, 21]. Plasma lyso-Gb3 levels are currently the most widely used biomarker in clinical practice and show partial correlation with disease severity. Nevertheless, this marker presents false negatives in female patients and those with extremely late-onset Fabry disease, as noted in previous studies [22]. Furthermore, lyso-Gb3 has shown poor correlation with clinical events in treated patients [23–25], underscoring the need for novel, specific biomarkers to improve the stratification and monitoring of Fabry patients. Although the existence of myeloid bodies in kidney tissue is important for the diagnosis of Fabry disease, this method is less applicable for early diagnosis. In this study, urinary sediment samples from 25 Fabry disease patients were analyzed, revealing the presence of urinary myeloid bodies in 21 patients (84%; 9 males and 12 females). The detection rate was consistent across genders, with no significant sex-based differences observed. Notably, urinary myeloid bodies were absent in healthy controls and patients with other renal diseases. Although previous studies have reported drug-induced phospholipidosis characterized by the presence of myeloid bodies in patients treated with cationic amphiphilic drugs [26], this study included 2 lupus nephritis patients on hydroxychloroquine therapy, and no urinary myeloid bodies were observed in their urinary sediment samples. These findings suggest that urinary myeloid bodies are not universally associated with the use of cationic amphiphilic drugs. Detailed medical history taking can help discern the etiology of urinary myeloid bodies, supporting their specificity to Fabry disease in this context.

Comparison between Fabry disease patients with and without urinary myeloid bodies revealed no statistically significant differences in serum creatinine, eGFR, 24-h urinary protein, α-Gal A, or Lyso-GL-3. These findings suggest that the presence of urinary myeloid bodies is clinically significant. Notably, all 4 patients under the age of 20 also exhibited a significant number of urinary myeloid bodies. Among those with urinary myeloid bodies, 50% did not have proteinuria, and 52% had preserved renal function, suggesting that urinary myeloid bodies may serve as noninvasive biomarkers for the early diagnosis of Fabry disease.

ERT is the primary treatment for Fabry disease, designed to replace deficient α-Gal A [27], reduce intracellular Gb3 accumulation, alleviate symptoms, and slow disease progression [28–31]. Early diagnosis and timely treatment are critical for improving patient outcomes. Proteinuria is a common marker used to evaluate kidney damage in Fabry disease and to guide the initiation of ERT. However, in patients with proteinuria exceeding 1 g/day, ERT has limited effectiveness in reversing podocyte damage [9, 32] or halting the progression of Fabry nephropathy [33, 34]. This highlights the need for markers that can assess kidney damage before proteinuria develops. Previous studies have demonstrated that myeloid bodies accumulate in podocytes as Fabry disease progresses and are particularly responsive to ERT [12]. In this study, 7 patients completed a 1-year course of ERT, which resulted in a significant reduction in both the number and area ratio of urinary myeloid bodies. These findings suggest that the excretion of myeloid bodies in urine could be a useful tool for predicting outcomes and managing Fabry disease.

There are limitations to be considered. Given the rarity of Fabry disease, this study included a relatively small sample size, limiting the ability to perform comparative analyses across different age-groups and genders within the Fabry disease population. Additionally, due to the invasive nature of renal biopsy, the study did not include sufficient tissue samples to investigate the correlation between myeloid bodies observed in renal tissues and those identified in urinary sediment. Finally, the excretion of urinary myeloid bodies may be influenced by patients' medication history, such as the use of cationic amphiphilic drugs [26, 35, 36], or could potentially be associated with other genetic disorders [37]. However, these associations can be distinguished through thorough medical history taking.

In conclusion, our study first provides a quantitative analysis of myeloid bodies in the urinary sediment of Fabry patients, highlighting their widespread presence and potential as biomarkers for early diagnosis of Fabry nephropathy and monitoring ERT efficacy. Future large-scale clinical studies are necessary to further explore the relationship between urinary myeloid body excretion and Fabry nephropathy.

Statement of Ethics

The study was conducted in accordance with the ethical guidelines of the 2013 Declaration of Helsinki, registered with the Chinese Clinical Trial Registry (Registration No. ChiCTR2400086448), and received approval from the IEC for Clinical Research of Zhongda Hospital, Affiliated to Southeast University (2023ZDSYLL054-P01). Written informed consent was obtained from all participants prior to study enrollment. This study includes children under the age of 18 and has obtained written informed consent from the participants' parent in the study.

Conflict of Interest Statement

All the authors declared no competing interests.

Funding Sources

This investigation was supported by Jiangsu Provincial Key Research and Development Program (BE2023770), Young Scholars of Yangtze River Scholar Professor Program (2023 BW), Research Personnel Cultivation Programme of Zhongda Hospital Southeast University (CZXM-GSP-RC150), Zhongda Hospital Affiliated to Southeast University, and Jiangsu Province High-Level Hospital Pairing Assistance Construction Funds (zdlyg02).

Author Contributions

Bin Wang, Xiaoliang Zhang, Aihua Zhang, Junlan Yang, and Zhiyuan Wei were responsible for the research idea and study design; Junlan Yang, Zhiyuan Wei, and Haifeng Ni were responsible for the formal analysis, Qianqian Wu, Siqi Peng, Wen Shi, Xiaoxu Wang, Yan Yang, Jianan Jiang, Jingyuan Cao, Yao Wang, and Liyuan Zhang were responsible for the investigation; Junlan Yang and Zhiyuan Wei wrote the original draft; and Bin Wang, Xiaoliang Zhang, and Aihua Zhang reviewed and edited the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author Bin Wang (wangbinhewei@126.com) upon reasonable request.

References

1 Wanner C, Arad M, Baron R, Burlina A, Elliott PM, Feldt-Rasmussen U, et al. European expert consensus statement on therapeutic goals in Fabry disease. Mol Genet Metab. 2018;124(3):189–203. https://doi.org/10.1016/j.ymgme.2018.06.004
2 Germain DP, Altarescu G, Barriales-Villa R, Mignani R, Pawlaczyk K, Pieruzzi F, et al. An expert consensus on practical clinical recommendations and guidance for patients with classic Fabry disease. Mol Genet Metab. 2022;137(1–2):49–61. https://doi.org/10.1016/j.ymgme.2022.07.010
3 Li X, Ren X, Zhang Y, Ding L, Huo M, Li Q. Fabry disease: mechanism and therapeutics strategies. Front Pharmacol. 2022;13:1025740. https://doi.org/10.3389/fphar.2022.1025740
4 Arends M, Wanner C, Hughes D, Mehta A, Oder D, Watkinson OT, et al. Characterization of classical and nonclassical Fabry disease: a multicenter study. J Am Soc Nephrol. 2017;28(5):1631–41. https://doi.org/10.1681/ASN.2016090964
5 Izhar R, Borriello M, La Russa A, Di Paola R, De A, Capasso G, et al. Fabry disease in women: genetic basis, available biomarkers, and clinical manifestations. Genes. 2023;15(1):37. https://doi.org/10.3390/genes15010037
6 Michaud M, Mauhin W, Belmatoug N, Garnotel R, Bedreddine N, Catros F, et al. When and how to diagnose Fabry disease in clinical pratice. Am J Med Sci. 2020;360(6):641–9. https://doi.org/10.1016/j.amjms.2020.07.011
7 Chinese National Expert Collaborative Group of Fabry Disease; China Medical Education Association Clinical Nephrology Committe. Multidisciplinary treatment in the long-term management of Fabry disease. Zhonghua Nei Ke Za Zhi. 2023;62(8):949–55. https://doi.org/10.3760/cma.j.cn112138-20230218-00095
8 Levstek T, Vujkovac B, Trebusak Podkrajsek K. Biomarkers of Fabry nephropathy: review and future perspective. Genes. 2020;11(9):1091. https://doi.org/10.3390/genes11091091
9 Braun F, Abed A, Sellung D, Rogg M, Woidy M, Eikrem O, et al. Accumulation of α-synuclein mediates podocyte injury in Fabry nephropathy. J Clin Investig. 2023;133(11):e157782. https://doi.org/10.1172/JCI157782
10 Lerario S, Monti L, Ambrosetti I, Luglio A, Pietra A, Aiello V, et al. Fabry disease: a rare disorder calling for personalized medicine. Int Urol Nephrol. 2024;56(10):3161–72. https://doi.org/10.1007/s11255-024-04042-4
11 Owens CL, Russell SD, Halushka MK. Histologic and electron microscopy findings in myocardium of treated Fabry disease. Hum Pathol. 2006;37(6):764–8. https://doi.org/10.1016/j.humpath.2006.01.021
12 Najafian B, Svarstad E, Bostad L, Gubler MC, Tøndel C, Whitley C, et al. Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease. Kidney Int. 2011;79(6):663–70. https://doi.org/10.1038/ki.2010.484
13 Katz SM, Lyons PJ. Urinary ultrastructural findings in Fabry disease. JAMA. 1977;237(11):1121–2. https://doi.org/10.1001/jama.1977.03270380065023
14 Murayama Y, Uchida M, Tojo A, Ishimitsu T. Electron microscopy of urinary sediments in Fabry disease. Kidney Int. 2018;94(4):834. https://doi.org/10.1016/j.kint.2018.04.010
15 Lenders M, Brand E. Fabry disease: a multisystemic disease with gastrointestinal manifestations. Gut Microbes. 2022;14(1):2027852. https://doi.org/10.1080/19490976.2022.2027852
16 Battaglia Y, Fiorini F, Azzini C, Esposito P, De Vito A, Granata A, et al. Deficiency in the screening process of Fabry disease: analysis of chronic kidney patients not on dialysis. Front Med. 2021;8:640876. https://doi.org/10.3389/fmed.2021.640876
17 Burlina A, Brand E, Hughes D, Kantola I, Krämer J, Nowak A, et al. An expert consensus on the recommendations for the use of biomarkers in Fabry disease. Mol Genet Metab. 2023;139(2):107585. https://doi.org/10.1016/j.ymgme.2023.107585
18 Tebani A, Mauhin W, Abily-Donval L, Lesueur C, Berger MG, Nadjar Y, et al. A proteomics-based analysis reveals predictive biological patterns in Fabry disease. J Clin Med. 2020;9(5):1325. https://doi.org/10.3390/jcm9051325
19 Slaats GG, Braun F, Hoehne M, Frech LE, Blomberg L, Benzing T, et al. Urine-derived cells: a promising diagnostic tool in Fabry disease patients. Sci Rep. 2018;8(1):11042. https://doi.org/10.1038/s41598-018-29240-w
20 Matafora V, Cuccurullo M, Beneduci A, Petrazzuolo O, Simeone A, Anastasio P, et al. Early markers of Fabry disease revealed by proteomics. Mol Biosyst. 2015;11(6):1543–51. https://doi.org/10.1039/c4mb00707g
21 Ducatez F, Mauhin W, Boullier A, Pilon C, Pereira T, Aubert R, et al. Parsing Fabry disease metabolic plasticity using metabolomics. J Pers Med. 2021;11(9):898. https://doi.org/10.3390/jpm11090898
22 Talbot A, Nicholls K, Fletcher JM, Fuller M. A simple method for quantification of plasma globotriaosylsphingosine: utility for Fabry disease. Mol Genet Metab. 2017;122(1–2):121–5. https://doi.org/10.1016/j.ymgme.2017.08.004
23 Bichet DG, Aerts JM, Auray-Blais C, Maruyama H, Mehta AB, Skuban N, et al. Assessment of plasma lyso-Gb(3) for clinical monitoring of treatment response in migalastat-treated patients with Fabry disease. Genet Med. 2021;23(1):192–201. https://doi.org/10.1038/s41436-020-00968-z
24 Kramer J, Weidemann F. Biomarkers for diagnosing and staging of Fabry disease. Curr Med Chem. 2018;25(13):1530–7. https://doi.org/10.2174/0929867324666170616102112

25 Beirão I, Cabrita A, Torres M, Silva F, Aguiar P, Laranjeira F, et al. Biomarkers and imaging findings of anderson-fabry disease-what we know now. Diseases. 2017;5(2):15. https://doi.org/10.3390/diseases5020015
26 Breiden B, Sandhoff K. Emerging mechanisms of drug-induced phospholipidosis. Biol Chem. 2019;401(1):31–46. https://doi.org/10.1515/hsz-2019-0270
27 Palaiodimou L, Kokotis P, Zompola C, Papagiannopoulou G, Bakola E, Papadopoulou M, et al. Fabry disease: current and novel therapeutic strategies. A narrative review. Curr Neuropharmacol. 2023;21(3):440–56. https://doi.org/10.2174/1570159X20666220601124117
28 Lee CL, Lin SP, Niu DM, Lin HY. Fabry disease and the effectiveness of enzyme replacement therapy (ERT) in left ventricular hypertrophy (LVH) improvement: a review and meta-analysis. Int J Med Sci. 2022;19(1):126–31. https://doi.org/10.7150/ijms.66448
29 van der Veen SJ, Hollak CEM, van Kuilenburg ABP, Langeveld M. Developments in the treatment of Fabry disease. J Inherit Metab Dis. 2020;43(5):908–21. https://doi.org/10.1002/jimd.12228
30 Kok K, Zwiers KC, Boot RG, Overkleeft HS, Aerts J, Artola M. Fabry disease: molecular basis, pathophysiology, diagnostics and potential therapeutic directions. Biomolecules. 2021;11(2):271. https://doi.org/10.3390/biom11020271
31 Felis A, Whitlow M, Kraus A, Warnock DG, Wallace E. Current and investigational therapeutics for Fabry disease. Kidney Int Rep. 2020;5(4):407–13. https://doi.org/10.1016/j.ekir.2019.11.013
32 Braun F, Blomberg L, Brodesser S, Liebau MC, Schermer B, Benzing T, et al. Enzyme replacement therapy clears Gb3 deposits from a podocyte cell culture model of Fabry disease but fails to restore altered cellular signaling. Cell Physiol Biochem. 2019;52(5):1139–50. https://doi.org/10.33594/000000077
33 Yonishi H, Namba-Hamano T, Hamano T, Hotta M, Nakamura J, Sakai S, et al. Urinary mulberry bodies as a potential biomarker for early diagnosis and efficacy assessment of enzyme replacement therapy in Fabry nephropathy. Nephrol Dial Transplant. 2021;37(1):53–62. https://doi.org/10.1093/ndt/gfaa298
34 Biancini GB, Jacques CE, Hammerschmidt T, de Souza HM, Donida B, Deon M, et al. Biomolecules damage and redox status abnormalities in Fabry patients before and during enzyme replacement therapy. Clin Chim Acta. 2016;461:41–6. https://doi.org/10.1016/j.cca.2016.07.016
35 Costa RM, Martul EV, Reboredo JM, Cigarrán S. Curvilinear bodies in hydroxychloroquine-induced renal phospholipidosis resembling Fabry disease. Clin Kidney J. 2013;6(5):533–6. https://doi.org/10.1093/ckj/sft089
36 Choung HYG, Jean-Gilles J, Goldman B. Myeloid bodies is not an uncommon ultrastructural finding. Ultrastruct Pathol. 2022;46(1):130–8. https://doi.org/10.1080/01913123.2021.2022054
37 Ni HF, Yang Y, Li CQ, Zhou TZ, Liu BC, Wang B. Myeloid bodies caused by COQ2 mutation: a case of concurrent COQ2 nephropathy and IgA nephropathy. Clin Kidney J. 2021;14(6):1697–700. https://doi.org/10.1093/ckj/sfab043