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Review

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Fabry nephropathy: focus on podocyte damage and therapeutic target

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Abstract

Fabry disease, a rare X-linked lysosomal storage disorder, is marked by a deficiency in the activity of the enzyme α-galactosidase A. This deficiency results in the accumulation of globotriaosylceramide (Gb3) within various tissues and organs, which leads to life-threatening complications and poor prognosis. Clinical manifestations are multisystemic, heterogeneous, and progressive. Early diagnosis and treatment are of great importance. Fabry nephropathy lesions are characterized by a cell vacuolization of glomeruli, tubules, interstitium, and arteries and by ultrastructural myelin bodies. Kidney injury can occur in various structures, with the podocytes being the first to be impacted due to their low regeneration and extensive exposure to Gb3. The accumulation of Gb3 causes injury to podocytes, which are essential components of glomerular cells, responsible for maintaining the integrity of the glomerular filtration barrier. Enzyme replacement therapy, dynamic monitoring of podocyte injury, and research on the repair and regeneration mechanism of podocyte injury will contribute to the overall treatment of kidney damage in Fabry disease and improve the renal prognosis.

Keywords: Fabry nephropathy, podocyte, treatment, regeneration

INTRODUCTION

Fabry disease (FD) is an inherited X-linked lysosomal storage disorder resulting from mutations in the GLA

gene. This gene is responsible for the production of α-galactosidase A (α-GalA) and leads to a potentially fatal buildup of globotriaosylceramide (Gb3) and relevant glycosphingolipids in tissues that contain lysosomes. The estimated prevalence of this condition ranges from 1 in 40,000 to 1 in 117,000 individuals[1]. In newborn screenings, the prevalence is underestimated, ranging from 1 in 8,882 to 1 in 12,500[2]. High-risk and family screening studies have revealed a higher frequency of FD than previously expected. Therefore, the estimated prevalence varies depending on the type of screening, such as family, newborn, non-dialysis-dependent chronic kidney disease patients, dialysis patients, and kidney transplant recipients[3]. FD can be categorized into two phenotypes: the classic and the non-classic. Classic FD primarily occurs in males, with almost complete deficiency of α-Gal A activity, and complications such as kidney, heart, and cerebrovascular issues appear earlier, leading to a poor prognosis. In contrast, the late-onset FD retains residual enzymatic activity, often manifesting as single-organ involvement, typically affecting the kidneys or heart[4].

Kidney complications are a predominant factor of morbidity and mortality in individuals with FD. The primary clinical presentations of renal involvement include proteinuria, hypertension, and progressive chronic kidney disease (CKD). Given that FD is a progressive disorder, it is essential for patients to receive a definitive diagnosis promptly, so that they gain early monitoring, supportive care, and suitable treatment options, which can prevent the onset of irreversible and potentially fatal complications. Since 2001, enzyme replacement therapy (ERT) has been the primary treatment for FD. This treatment aims to stabilize the condition, prevent the progression of organ damage, and alleviate disease symptoms. In addition, a chaperone therapy known as migalastat (Galafold®, Amicus) was approved for use in certain FD patients in the European Union in 2016 and subsequently in the United States in 2018[5].

Podocytes are primary targets in Fabry nephropathy [Figure 1]. The accumulation of Gb3 causes injury to podocytes, which are essential components of glomerular cells, responsible for maintaining the integrity of the glomerular filtration barrier. In pediatric renal biopsies, the deposition of Gb3 within renal cells and the podocyte foot process effacement can be detected, preceding the clinical onset of pathological albuminuria. Previous studies have demonstrated that podocytes in Fabry nephropathy accumulate the most Gb3, leading to the early occurrence of (micro)albuminuria[6,7]. Given the restricted ability to regenerate, podocyte damage and loss are regarded as pivotal events in the pathophysiology of kidney disease, making them prime targets for therapeutic intervention. Inflammation also plays a significant pathogenetic role in FD. Accumulated Gb3 in lysosomes results in the accumulation of impaired organelles and protein aggregates, which initiate inflammation and oxidative stress. This initiates the synthesis of extracellular matrix proteins to facilitate tissue repair. However, if uncontrolled, this reparative response can evolve into a pathological state, causing excessive protein accumulation and renal fibrosis[8]. In this work, we offer a comprehensive review of Fabry nephropathy, with a particular focus on kidney podocyte lesions and treatment options.

CLINICAL FEATURES OF FABRY NEPHROPATHY

Kidney involvement occurs in 55% of Fabry disease patients[9]. Albuminuria and estimated glomerular filtration rate (eGFR) are the definitive indicators for tracking kidney conditions associated with FD [Table 1] Proteinuria is usually a manifestation of podocyte injury and urinary protein excretion is closely linked to renal function progression. In males with classic FD, pathological albuminuria often appears between the ages of 20 and 30 years and serves as an independent risk factor for the worsening of kidney conditions[4]. Wanner *et al.* demonstrated that individuals experiencing rapid kidney disease progression had notably elevated average ratios of urinary protein to urinary creatinine compared to those with slower progression (1.5 *vs.* 0.2 for men; 1.4 *vs.* 0.5 for women; $P < 0.0001$)[10]. Kidney function normally declines over time and can cause end-stage renal disease (ESRD) in almost all classic male patients and some female

Table 1. Clinical manifestation of Fabry nephropathy

Laboratory examination	Clinical manifestation
Urinalysis	Microalbuminuria in early phases, then progress to moderate to severe proteinuria in adulthood
	Hematuria
Kidney function	Glomerular hyperfiltration is an early marker, then a progressive decrease in GFR
Urine microscopy	Mulberry cells with characteristic "Maltese cross bodies", podocyturia
Tubular dysfunction	α1-microglobulin, N-acetyl-β-glucosaminidase, and alanine aminopeptidase were elevated in early phases, isosthenuria, distal renal tubular acidosis
Ultrasound findings	Renal cysts, mainly parapelvic ones

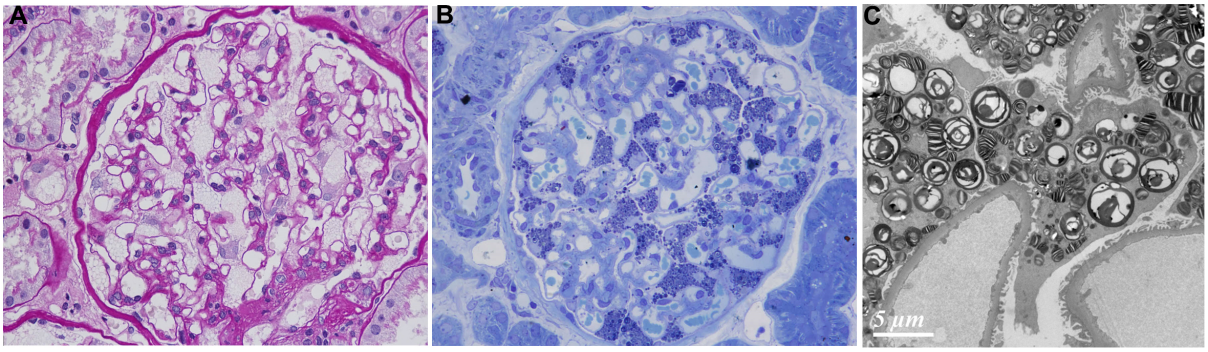

Figure 1. (A) The typical pathological manifestations of glomerulus in Fabry disease under light microscope. Vacuole-like changes in the cytoplasm of podocytes and parietal epithelial cells were observed. (Periodic Acid-Schiff stain, ×400 times); (B) The typical pathological manifestations of glomerulus in Fabry disease under light microscope. A large number of Gb3 bodies were deposited in the cytoplasm of podocytes and parietal epithelial cells, and toluidine blue staining was observed. (×400 times); (C) Typical glomerular pathological manifestations of Fabry disease under electron microscope. A large number of "zebra bodies" formed by Gb3 deposition in the cytoplasm of podocytes and foot process segmental fusion.

patients. Heterozygous females often show no symptoms, but they can still develop a severe form of the condition similar to males. The variability of female presentations is due to the inactivation of one chromosome X in different tissues and organs. The processes are more complex than the simple random inactivation, with factors such as skewed inactivation patterns and DNA methylation of GLA being significant considerations[11,12]. Multiple studies have confirmed that the MSSI score effectively distinguishes FD from various other critical illnesses and is a reliable measure for evaluating the severity of the pain. Zhang *et al.* found that the MSSI score was notably elevated in FD patients with a decline in renal function compared to those with stable kidney function[13]. This score emerged as an independent predictor for accelerated progression of Fabry nephropathy, frequently leading to dialysis or ESRD.

PATHOLOGICAL FEATURES AND PATHOGENESIS

Kidney biopsy offered crucial insights that were not accessible from standard evaluations of renal function and proteinuria levels, underscoring the significance of renal biopsy as an initial assessment tool for all individuals with Fabry disease, regardless of the severity of clinical presentation. Kidney biopsies can identify and measure Gb3 deposits in individuals with a 30-300 mg/g albumin-to-creatinine ratio and normal renal function. For women without signs of FD-related kidney disease, substantial renal deposits could indicate the need to initiate specific treatment[14]. Fogo *et al.* developed a standardized biopsy scoring system for disease-specific lesions and general progression lesions in kidney biopsies, revealing a range of histological changes in the early stages of Fabry nephropathy. This underscores the importance of kidney biopsies for baseline assessments, even in cases with minimal clinical manifestations[15]. The initial damage

in Fabry disease stems from the accumulation of glycolipids in nearly all types of cells within the glomerulus, with particularly large accumulations in podocytes. These deposits are not confined to the glomerular cells but are also found within the tubular cells and the endothelium of the peritubular capillaries[16]. The progression of kidney disease is primarily characterized by podocyte damage, persistent proteinuria, and permanent damage to the small blood vessels within the kidneys, leading to progressive glomerulosclerosis, capillary wall thickening, tubular atrophy, interstitial fibrosis, and arterial and arteriolar sclerosis. Several studies showed glomerulosclerosis and segmental sclerosis levels are sensitive indicators for the kidney progression of patients with FD[13,17].

Gb3 deposits in podocytes have drawn particular attention from researchers. On light microscopy, vacuoles were frequently observed in podocytes. Electron microscopy revealed that the Gb3 accumulations within the cells manifested as distinctive osmiophilic inclusions in the podocytes' cytoplasm, exhibiting a pattern of alternating light and dark concentric rings. These osmiophilic myelin bodies had a diameter ranging from 1 to 3 nm and presented a "zebra-like" pattern [Figure 1]. Effacement of the segmental foot processes was also found in the podocytes. Using quantitative morphometric electron microscopic studies, it was indicated that the proportion of podocyte cytoplasm filled with Gb3 deposits rises with age but stabilizes after the age of 27. This implies that there exists a critical level of Gb3 accumulation beyond which podocytes may sustain injury and loss[18]. Indeed, podocyturia (loss of podocytes through the urine) in Fabry nephropathy has been generally examined and is considered an indicator of early kidney involvement in FD[19].

The accumulation of Gb3 can lead to its conversion into globotriaosylsphingosine (lyso-Gb3), a process likely facilitated by the non-specific action of lysosomal acid ceramidase that cleaves the fatty acid from Gb3. Elevated lyso-Gb3 levels in the plasma of FD patients suggest that it is a more reliable biomarker for tracking disease progression compared to plasma Gb3 levels[20]. In cultured podocytes, Lyso-Gb3 triggered the activation of Notch1, leading to an increase in the production of tumor growth factor β1 (TGF-β1), which facilitates the development of fibrosis and sustained inflammation by the synthesis of extracellular matrix in renal cells via epithelial-to-mesenchymal transition[21]. Another study found that human podocytes respond to lyso-Gb3 by initially increasing the expression of genes for the αvβ3 integrin and uPAR. The αvβ3/UPAR system plays a pivotal role in the detachment of podocytes and the subsequent release of these cells in the urine, a process known as podocyturia[22]. Analyses utilizing transcriptome connectivity mapping and SILAC quantitative proteomics showed the deposits of α-synuclein (SNCA) as a critical factor in podocyte damage. Suppressing SNCA through genetic and pharmacological interventions may enhance the lysosomal structure and functionality in Fabry podocytes[23].

CURRENT TREATMENT

Enzyme replacement therapy

Since 2001, ERT has been available as a specific treatment option to compensate forαGalA deficiency[24] [Table 2]. At present, three formulations of recombinant human αGalA are accessible: agalsidase α (Replagal®), agalsidase β(Fabrazyme®), and a biosimilar of agalsidase β (JR-051). Agalsidase α is manufactured using a human cell line and administered at a dosage of 0.2 mg/kg, with an infusion duration of 40 min. Agalsidase β is derived from Chinese hamster ovary cells, with a suggested dosage of 1.0 mg/kg and a standard infusion time of approximately 240 min. At present, there is no strong data showing the superiority of either one for treating FD[25]. ERT has been demonstrated to significantly mitigate the impact of FD on the heart, kidneys, and nervous system[26]. Initiating ERT as early as possible may be beneficial. For classical male patients, ERT should be begun upon diagnosis; heterozygous females and atypical male patients are recommended to initiate ERT at the onset of clinical manifestations of FD. However, the efficacy of ERT is less satisfactory in patients with advanced kidney disease and severe cardiac fibrosis[26].

Table 2. Potential effects of enzymatic and supportive therapy on podocytes

Treatments	Effects on podocytes
Enzyme replacement therapy	A reduction in Gb3 levels within podocytes
Chaperone therapy	Reduced Gb3 deposits on podocytes
SNCA inhibitor	Improve lysosome podocyte structure and function
ACEI/ARB	Decrease progressive kidney disease by alleviating podocyte injury
SGLT2 inhibitors	Alleviate podocyte damage by targeting the pathogenetic mechanisms, such as oxidative stress and inflammation

Data from the Fabry Outcome Survey (FOS) indicated that early initiation of ERT with agalsidase α can slow renal function deterioration and improve symptoms, and it also underscored the sustained efficacy and safety of ERT in FD patients[27]. Sustained administration of agalsidase β has been demonstrated to effectively clear Gb3 from mesangial and glomerular endothelial cells[28]. A dose-dependent clearance of Gb3 in podocytes was also reported[28]. Research by Nowak *et al.* indicated that the licensed dosage of Agalsidase β outperforms Agalsidase α in lowering Lyso-Gb3 levels among patients with classic FD[29]. However, Arends *et al.* confirmed the higher prevalence of neutralizing anti-drug antibodies (ADAs) in patients treated with agalsidase β[30]. Long-term ERT can result in the production of ADAs, which diminishes the therapeutic effectiveness of ERT by altering the catalytic function of the enzyme and cellular uptake to hasten the deterioration of renal function. Therefore, no conclusive evidence to show that one enzyme is superior to another during nearly two decades of ERT treatment. The choice between β and α enzymes often depends on individual responses and specific clinical contexts

Chaperone therapy

Migalastat, a pharmaceutical chaperone, has gained approval as the first oral medication for FD since 2016. It is specifically indicated for patients with amenable mutations, predominantly those with attenuated, late-onset forms of the disease who retain significant residual enzyme activity. Individuals with these genetic variants rarely have severe renal disease, resulting in minimal or absent podocyte impairment[31]. Migalastat is a derivative of 1-deoxygalactonojirimycin and acts as a structural stabilizer for the terminal galactose of Gb3, enhancing susceptible mutant forms of the α-Gal A enzyme. Additionally, this compound increases and stabilizes the lysosomal activity[32], promoting the transport of susceptible mutant α-Gal A from the endoplasmic reticulum to lysosomes. The enhancement of kidney and heart function, coupled with increased α-Gal A enzyme activity and reduced Gb3 deposits after chaperone therapy, indicated that migalastat could be a practical therapeutic choice and a secure substitute for ERT among FD patients[33]. Moreover, the capability of migalastat to penetrate the blood-brain barrier is promising, and its efficacy on neurological symptoms remains to be confirmed in upcoming studies.

Developing treatments

Substrate reduction therapies function by decreasing the synthesis of accumulated substrate caused by the lack of α-Gal A activity. A principal benefit of these treatments is their effectiveness regardless of the specific genetic mutation causing the enzymatic deficiency. Notably, they can be used as a standalone treatment or in conjunction with ERT[34].

Pegunigalsidase alfa represents a pegylated variant of the α-Gal A, produced through plant cell culture techniques, and is recently approved in the European Union and United States for the treatment of FD. In terms of efficacy outcomes, kidney biopsies from patients administered pegunigalsidase alfa showed a marked decrease in Gb3 levels, and their renal function was stable[35]. Multiple phase-3 clinical trials are either actively in progress, such as the BALANCE study [NCT02795676], or have recently concluded, including the BRIGHT study [NCT03180840] and the BRIDGE study [NCT03018730].

Gene therapy operates on the principle of introducing DNA that encodes the α-Gal A protein into the patient's cells. Introducing a therapeutic gene, along with subsequent endogenous cellular expression, will facilitate the production of the enzyme that was originally scarce, potentially altering the course of FD fundamentally[36]. Currently, phase 1/2 clinical trials are exploring the use of *in-vivo* gene therapy with various biological agents, including adeno-associated virus vectors and non-viral vectors.

Research has shown that although ERT can reduce Gb3 accumulation in podocytes, its effect on podocyte damage repair is not obvious[23]. In addition, the CRISPR/Cas9-mediated knockout of alpha galactose glucoside enzyme of Sertoli cell model confirmed that although ERT can reverse the accumulation of Gb3, it does not solve the problem of lysosome dysfunction[37]. Further transcriptome and quantitative proteomic analysis found that SNCA accumulation is the key factor in podocyte damage[23]. Genetic and pharmacological inhibition of SNCA can improve the structure and function of lysosomal podocytes in Fabry disease, demonstrating an effect that surpasses that of ERT[23,38].

In addition, it has been suggested that podocyte injury in Fabry disease is related to the dysregulation of the autophagy pathway. In podocytes, upregulation of the autophagy marker microtubule-associated protein 1 light chain 3 (LC3-II) was observed, which may be related to defects in mTOR and AKT signaling pathways[39]. mTOR is a key negative regulator of autophagy formation, and AKT is its upstream regulator, both of which show reduced activity in Fabry disease[39]. Reduced mTOR phosphorylation results in a rise in autophagosomes. However, the continuous overactivation of autophagy can cause podocyte injury. Li *et al.* proposed that a negative feedback loop might exist, where the surge in autophagosomes could reactivate mTOR[40]. This reactivation would suppress further autophagosome creation and promote lysosomal regeneration, possibly serving as a cellular defense against autophagy-induced cell death[40]. Accumulation of Gb3 impairing mitochondrial function can disrupt mTA1 activity, causing spontaneous effects and energy deficits. Therefore, mTOR-dependent pathways are pivotal in regulating autophagic-lysosomal fusion and mitochondrial function. Disruption of the lysosome-autophagy-mitochondria axis is a significant factor in the organ damage associated with FD[41]. Additionally, this interaction may also offer a new direction for treating podocyte damage in Fabry disease[39].

Supportive therapy

Controlling proteinuria is crucial for maintaining renal function in FD patients. Medications such as angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) have been shown to slow the progression of renal disease in FD by reducing damage to podocytes[42,43]. Warnock *et al.* demonstrated individuals who sustained a UP/Cr ratio < 0.5 g/g or a 50% reduction from their initial UP/Cr ratio through the use of an ACEi or ARBs experienced a less decline in eGFR (-3.6 mL/min), in contrast to those who failed to reach these criteria (-7.0 mL/min)[43].

Initially developed to reduce blood glucose levels, SGLT2 inhibitors have become increasingly recognized for their role in CKD management. Recently, SGLT2 inhibitors have gained approval for treating CKD progression in patients with proteinuria. Battaglia *et al.* suggested that SGLT2 inhibitors can mitigate damage to podocytes by targeting the pathogenetic mechanisms like oxidative stress and inflammation that ERT or chaperone therapy alone might not fully resolve[44]. This study is the first to assess the effect of Dapaglifozin in FD patients with albuminuria and renal function progression.

PODOCYTE REGENERATION

Professor Romagnani from Italy, as early as 2013 after a series of research results, accurate account of the inherent in the human renal unit cells, especially the glomerular cells and renal tubular epithelial cells of

progenitor cell source, positioning and differentiation problem[45]. During the embryonic stage, these renal progenitor cells are located in the renal utricle and S-shaped bodies and retain the ability to differentiate into both glomerular and tubular epithelial cells. During subsequent development, the number of RPCs decreases, and at the adult stage, RPCs only account for about 2% of the innate cells in the kidney. As RPCs of podocyte, only exists in the bowman's capsule wall, at the same time expressing cells and associated RPCs differentiation markers.

Podocyte regeneration for repair and functional recovery after kidney damage is of crucial importance. In the last decade, notable progress has been made in the study of podocyte regeneration. For example, it has been shown that by enhancing the differentiation capacity of renal precursor cells, podocyte regeneration can be enhanced, leading to improved prognosis in chronic kidney disease[46]. In addition, some studies have also discussed the effects of specific drugs such as BIO (GSK3 inhibitor) on cell regeneration[47].

In Fabry disease, the loss of αGalA activity leads to the accumulation of metabolic substrates in podocytes and other cells, which may affect the normal function and regeneration ability of podocytes. Therefore, therapeutic strategies targeting podocyte regeneration may have some potential for the treatment of renal involvement in FD. However, the specific mechanism of the interaction between FD and podocyte regeneration is not fully understood at present, and further studies are needed to elucidate it.

As research on kidney damage markers advances in both theory and methodology, the evaluation of tissue damage using non-invasive biomarkers has gained significant attention in recent years. Small molecules, such as those found in blood and urine tests, are explored, including urine concentrations of dissolved Gb3 in Sertoli cells or the detection of glomerular progenitor cells in urine. At the ERA - EDTA 2024 academic conference, a study by Ugalde-Altamirano *et al.* from Spain reported that RPCs detected in urine could serve as early non-invasive markers for evaluating kidney damage in Fabry patients[48]. The study investigated the correlation between RPCs and Gb3 accumulation in relation to the severity of renal tissue injury. The research involved Fabry disease patients, healthy controls, and chronic kidney disease (CKD) patients without Fabry disease. RPCs were isolated from urine using specific markers and flow cytometry, and their association with renal function indicators and the level of proteinuria was analyzed. The study found that labeled RPCs were difficult to detect in the urine of healthy individuals, while their numbers significantly increased in the urine of Fabry disease patients and those with biopsy-proven CKD. Additionally, the number of RPCs correlated with the degree of proteinuria. This research identified, for the first time, glomerular-specific progenitor cells with Gb3 accumulation in the urine of Fabry patients, indicating their potential as biomarkers for early kidney injury in this disease. The findings suggest that therapeutic strategies aimed at podocyte regeneration may emerge as a new direction for future research in Fabry disease, potentially improving renal prognosis for patients.

CONCLUSION

FD is a lysosomal storage disease that can affect multiple organs and presents diverse and non-specific clinical manifestations. Among the histological features of renal involvement, podocyte lesions are the most severely affected. Early ERT can delay disease progression and improve prognosis. The implementation of a new dynamic monitoring mechanism for podocyte injury, along with the expanded concept of cell repair and regeneration therapy, combined with comprehensive interdisciplinary symptom management, offers an optimistic outlook for the prognosis of patients with renal impairment due to FD.

DECLARATION

Authors' contributions

Concept and design of the review,and drafting: Zhang D
Literature collection: Xie K
Revising the manuscript: Zhang J
All authors read and approved the final version of the manuscript.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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