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# Fabry Disease: Update, Focusing on Heart Disease by Multimodal Imaging

**Adrian Espejel-Guzman[1], Emily Rodríguez[1], Valente Fernandez-Badillo[1], Javier Serrano-Roman[1], Aldo Cabello-Ganem[1], Alexis Daniel Aparicio-Ortiz[1], Alberto Ramon-Rios[1], Mariali Palacios-Cruz[1], Nilda Espinola-Zavaleta[1,2*]**

[1]Department of Nuclear Cardiology. National Institute of Cardiology Ignacio Chavez, Mexico City, Mexico
[2]ABC Medical Center, IAP, Department of Echocardiography, Mexico City, Mexico
Email: *niesza2001@hotmail.com

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## Abstract

Fabry disease (FD) is a rare X-linked lysosomal accumulation disorder caused by a deficiency in the enzyme alpha-galactosidase A ($\alpha$Gal A), resulting in excessive storage of glycosphingolipids, particularly globotriaosylceramide (Gb3). This leads to cellular dysfunction in various organs, with cardiovascular compromise being the major cause of morbidity and mortality. This study aimed to provide a comprehensive overview of FD focusing on its genetic, epidemiological, clinical, diagnostic, and therapeutic aspects. This study explored the genetic mutations associated with FD, its epidemiology, clinical phenotypes, cardiac manifestations, diagnostic approaches, and current treatment options. **Background:** FD is caused by mutations in GLA on the X chromosome, with over 1000 identified variants. Neonatal screening and specific studies have shown an increased incidence of FD. The clinical presentation varies between classic and late phenotypes, with cardiac involvement being a major concern, particularly in late-onset FD. **Purpose:** This study aimed to summarize the current knowledge on FD, emphasizing cardiac involvement, diagnostic modalities, and treatment options. **Methods:** A literature review of relevant studies on FD, including genetics, epidemiology, clinical presentation, diagnostic methods, and treatment options, was conducted. **Results:** Cardiac manifestations of FD included left ventricular hypertrophy (LVH), heart failure, arrhythmias, and sudden death. Diagnostic approaches such as electrocardiography, echocardiography, and cardiac magnetic resonance imaging play crucial roles in the early detection and monitoring of cardiac involvement. Enzyme replacement therapy (ERT) and emerging treatments have shown promise in managing FD, although challenges remain. **Conclusions:** FD remains a challenging condition in cardiology, with under-diagnosis being a concern. Early detection and specific therapy are essen-

tial to improve patient outcomes. Echocardiography and cardiac MRI are valuable tools for diagnosis and follow-up. Despite the advances in treatment, accessibility remains an issue. More research is needed to deepen our understanding of FD and to improve therapeutic strategies.

## Keywords

Fabry Disease, Hypertrophic Cardiomyopathy, Echocardiography, Cardiac Magnetic Resonance Imaging, Enzyme Replacement Therapy

## 1. Introduction

### 1.1. Definition

Fabry disease (FD), is an X-linked lysosomal accumulation disease that appears due to a deficiency of the enzyme alpha-galactosidase A (*α*Gal A), responsible for the degradation of glycosphingolipids, such as globotriasylceramide (Gb3). This deficiency results in the excessive storage of Gb3, which leads to cellular dysfunction in different organs and is currently the main cause of progression and death [1]. Cardiac damage generally manifests as left ventricular hypertrophy (LVH), myocardial fibrosis, arrhythmias, heart failure (HF), and sudden death, leading to rapid clinical degeneration [2]. Recent research has allowed the implementation of different therapeutic methods, such as enzyme replacement therapy (ERT), and new drugs that are still under approval have made great progress, suggesting that myocardial inflammation is the focus of future research [1] [2].

### 1.2. Epidemiology

Incidence FD could rise to 1 per 3000 due to the increase in the incidence of cases for the implementation of neonatal screening in recent years, as well as specific studies in high-risk patients (unexplained LVH or dialysis patients) [3].

The prevalence in white male populations ranges approximately between 1:17,000 and 1:117,000 [4] [5].

### 1.3. Genetics

FD is caused by genetic mutations in the GLA gene on the X chromosome (Xq22.1), of which over 1000 have been identified [2]. The main variants associated with cardiovascular alterations and compromise were p.N2155, IVS4b919GA, and p.F113L.

### 1.4. Clinical Presentation: Classic and Late Phenotypes

FD can present in two different clinical forms: classic and non-classic or late [5] [6]. The classic form is the most severe and is associated with pathological genetic variants that lead to very low (<3%) or non-existent enzymatic activity, in

addition to presenting, for the most part, multiorgan clinical manifestations (Figure 1(A)). Late-onset FD is characterized by being less severe and variable, where enzyme activity tends to be less than 30% and clinical manifestations are usually limited to a specific organ, particularly the heart and kidneys (Figure 1(B)) [7]. Most commonly, heart damage in FD occurs in the late phenotype, in which patients may not present symptoms until age 50, when they develop cardiomyopathy [6] [7] [8].

Heart Condition

LVH and HF were the most frequent findings, followed by arterial hypertension, angina pectoris, and acute myocardial infarction, although the latter were

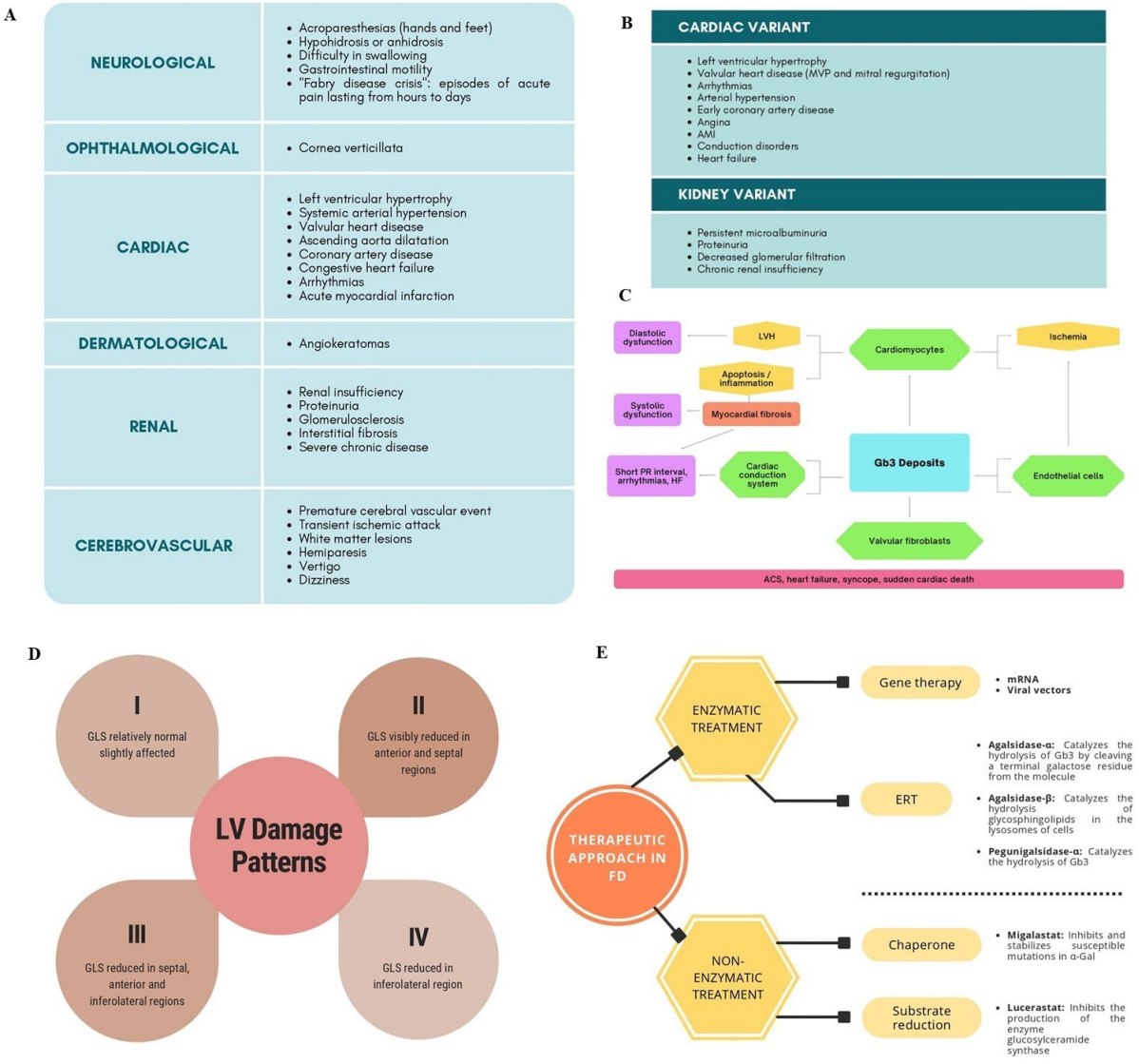


**Figure 1.** A. Clinical manifestations present in Fabry disease. B. Main clinical characteristics of cardiac and renal variants. C. Pathophysiology of cardiac damage in Fabry disease. D. Left ventricular damage patterns by global longitudinal strain. E. Therapeutic approach to Fabry disease. Abbreviations: MVP, mitral valve prolapse; AMI, acute myocardial infarction; Gb3, globotriaosylceramide; LVH, left ventricular hypertrophy; HF, heart failure; ACS, acute coronary syndrome; GLS, global longitudinal strain; ERT, enzyme replacement therapy.

less frequent and appeared late. Cardiac involvement usually manifests between 20 and 40 years of age and is characterized by progressive hypertrophy and diastolic dysfunction of the left ventricle (LV) in addition to microvascular damage and Gb3 infiltration, leading to restrictive pathophysiology and concentric hypertrophy (**Figure 1(C)**) [8] [9] [10]. Sudden cardiac death and ventricular tachycardia (VT) represent the main causes of mortality in FD, accounting for 62% and 15.3%, respectively [11] [12].

LVH correlates with $\alpha$-galactosidase activity levels. Concentric LVH is the most common pattern of hypertrophy, and other patterns have been described, including concentric, apical, septal, and eccentric patterns. Also, LV outflow tract obstruction is infrequently (11 frontiers taube averbuch).

Patients are at particular risk of atrial fibrillation due to both left atrial dilatation and dysfunction [11].

## 2. Diagnostic Approach

### 2.1 Electrocardiography (ECG)

In the first instance, the finding of short PR and repolarization disorders is a characteristic manifestation of pre-hypertrophic diagnosis [9]. T-wave inversion in precordial leads and electrocardiographic data of LVH are present when cardiomyopathy has already developed, which, together with sinus bradycardia and AV conduction disorders, has a worse prognosis [2]. Other arrhythmias, such as atrial fibrillation and ventricular tachycardia (VT), occur in 30% - 40% of patients with preserved LV function, even without LVH or absence of valvular heart disease [10] (**Figure 2(A)**).

### 2.2. Echocardiography

Echocardiography is important for the detection and monitoring of cardiomyopathy, obstruction of the LV outflow tract (LVOTO), right ventricular hypertrophy (RVH), valvular abnormalities, hypertrophy of the papillary muscles, and LVH [13].

a) Left ventricular hypertrophy

LVH is the most typical and characteristic finding in FD, occurring in 46 - 61% of men and 18% - 28% of women [14] [15]. Progression towards myocardial fibrosis usually occurs 10 years earlier in women [15]. It is now accepted that an unexplained LV wall thickness >12 mm and an LV index mass >95 g/m$^2$ in women and >115 g/m$^2$ in men are compatible with LVH and FD, where hypertrophy is typically concentric, although it can also appear as eccentric, apical, and septal asymmetry [16].

b) Abnormalities in LV function

LVH together with progressive diastolic dysfunction is the main cause of cardiac degeneration in FD in up to 64.4% of patients [17], which explains why patients with FD in early stages have heart failure (HF) with preserved LV ejection fraction (LVEF) [14].

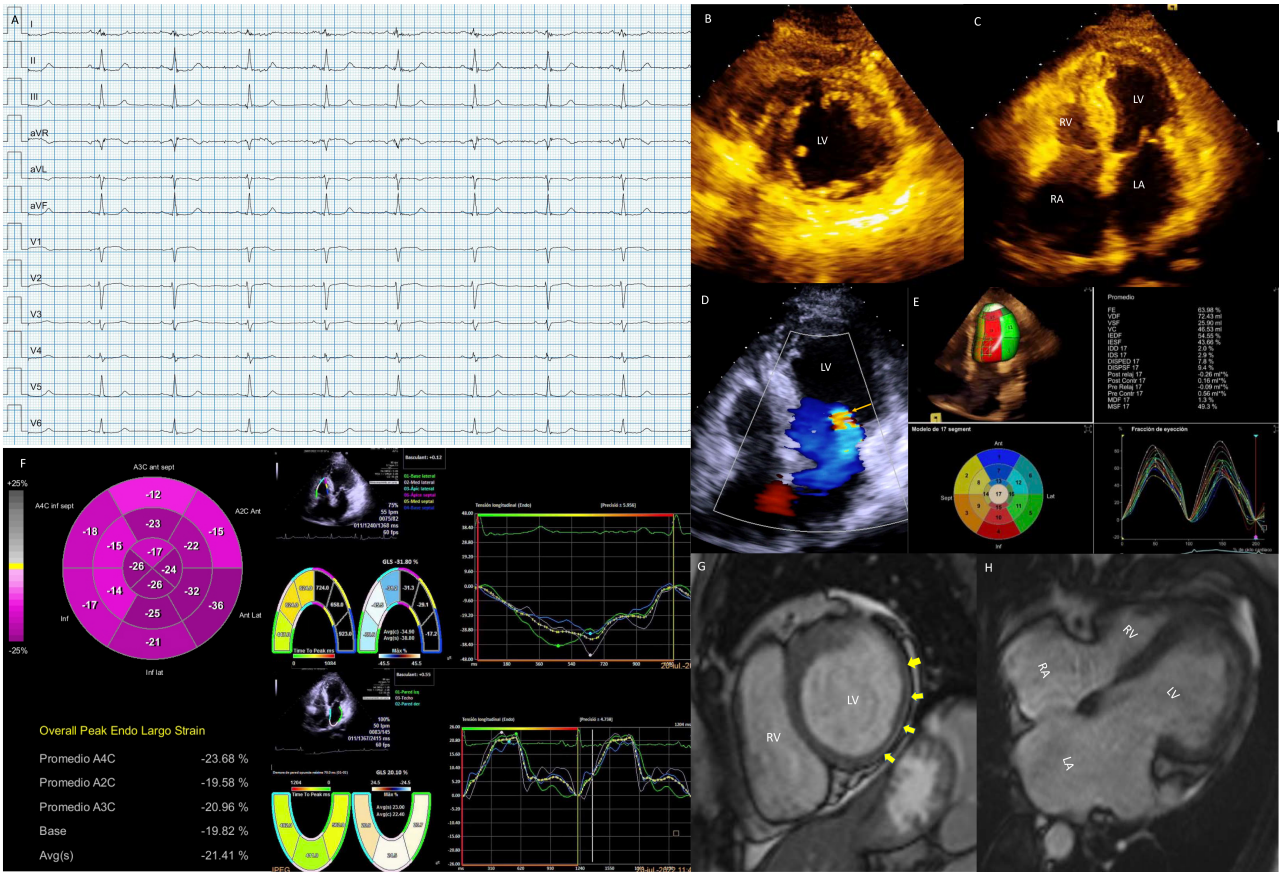


**Figure 2.** A. 12-lead electrocardiogram shows sinus rhythm with HR of 53 bpm. Hemiblock of the posterior fascicle of the left bundle branch of His. 2D and 3D transthoracic echocardiogram. B. Parasternal short axis view at the level of the papillary muscles with hypertrophy of the interventricular septum. C. Apical 4-chamber view with biatrial enlargement, normal ventricular diameters, and septal hypertrophy. D. Color Doppler in the apical 4-chamber plane shows moderate mitral regurgitation (orange arrow). E. Left ventricular ejection fraction of 64%. Overall longitudinal strain. F. Longitudinal global strain of the left ventricle with a type 3 pattern. Normal longitudinal strain of the free wall of the right ventricle (−34%), and global strain of the left atrium and of the reservoir phase decreased (22.40% and 22.35%, respectively). Cardiac MRI. G. The gadolinium-enhanced sequence shows a non-ischemic pattern in the basal third: transmural in the anteroseptal segment, subendocardial in the anterior, anterolateral intramyocardial and inferoseptal (yellow arrows). H. 4-chamber image showing biatrial enlargement and ventricles with diameters within normal parameters. Abbreviations: RA-right atrium; RV-right ventricle; LA-left atrium; LV-left ventricle.

Analyses of echocardiographic data from studies that investigated FD among unexplained LVH or late-onset HCM patients showed that FD occurs more frequently in concentric LVH than in asymmetric LVH patients [18]. Finally, HF with reduced LVEF usually occurs in the most advanced stages of the disease, and in only 6.7% of patients [18] [19]. It has been detected by tissue Doppler at the level of the mitral annulus that the lateral and septal values of S' and e' have high sensitivity and specificity for the diagnosis of FD, even in the absence of LVH [16].

c) LV outflow tract obstruction

Massive LVH involving the papillary muscles can cause LVOTO in 43% of cases, mainly in men with the classic phenotype of the disease, a late diagnosis of FD, and severe LVH. In Fabry cardiomyopathy, LVOTO mimicking hyper-

trophic cardiomyopathy is a very rare finding with few cases reported and successfully treated with cardiac surgery [20] [21].

d) Valvular abnormalities

Valvular heart disease can occur in up to 15% of patients with FD [16]. The left valve was particularly compromised. These echocardiographic findings are of little clinical significance and manifest with mild regurgitation, both mitral (57%) and aortic (47%) [6].

e) RV hypertrophy

RVH is mostly related to advanced stages of FD, in addition to its direct relationship with LVH. RVH tends to manifest with the same prevalence in both men and women (40% - 70%). In addition, the systolic function of the right ventricle was preserved in up to 50% of cases [22]. Despite normal echocardiographic parameters, both the free wall longitudinal strain and RV global strain may decrease by up to 41% and 35%, respectively [16].

f) Papillary muscle hypertrophy

LV papillary muscle hypertrophy is one of the most important echocardiographic signs of FD, in addition to being associated with hyperechogenicity and abnormalities in the structure and function of the mitral valve [23].

g) Binary sign

The binary sign is characterized by a hyperechoic surface of the LV endocardial border, resulting from intense glycolipid deposition in smooth muscle cells, followed by a hypoechoic subendocardial space with free glycosphingolipids, and finally an inner layer representing visibly affected myocardium [22] [23] [24] [25].

h) Usefulness of speckle tracking by echocardiography

Speckle tracking echocardiography (STE) has been shown to have greater sensitivity and specificity in establishing differentiation between lysosomal storage diseases [22]. Global longitudinal strain (GLS) is altered in patients with LVH and is an important indicator, particularly in women [19]. A study showed that the isovolumetric diastolic strain rate (SR) together with the systolic longitudinal strain (LS) are especially effective for the diagnosis of FD with preserved LVEF. The diagnostic scope of STE has made it possible to recognize at least four patterns of LV damage in patients with FD (**Figure 1(D)**), with a greater tendency towards basal inferoseptal LV involvement [26]. In addition, it has been observed that circumferential strain (CS) is decreased in FD, so a decrease in CS can distinguish between people with FD-prehypertrophic compared to healthy people [27] (**Figure 2(B)-(F)**).

## 2.3. Cardiac Magnetic Resonance Imaging (CMRI)

A significant advantage of MRI over echocardiography in the diagnosis of FD is that it allows a more precise assessment of LV thickness and the degree of hypertrophy [22] [28]. In addition, MRI facilitates the evaluation of the LV papillary muscles, an important aspect in the diagnosis of advanced stages of FD, since hypertrophy of these muscles is the main factor that contributes to the to-

tal thickness of the LV [29].

a) T1 and T2 mapping

In FD, excessive storage of sphingolipids in the cells causes a reduction in T1 (50%), even in patients without hypertrophy, which represents an advantage for early diagnosis [30]. This allowed us to observe a significant decrease in the T1 parameters due to an excess of cardiac glycosphingolipids in the early stages of FD [28] [31].

The elevation of T2, mainly in the basal inferolateral region, suggests that the myocardial pathological process of FD is influenced by inflammation; thus, a significant reduction in T2 after a therapeutic process for FD can be considered useful for monitoring and disease progression [22] [32].

b) Late gadolinium enhancement (LGE)

LGE is an important risk marker for HCM, which predicts cardiac pathological events. LGE reflects the presence of fibrosis and tends to occur in the basal and middle inferolateral portions of the LV [22] [33] (**Figures 2(G)-(H)**).

## 3. Treatment and Expectations for the Future

Currently, first-line treatment for FD is based on enzyme replacement therapy (ERT) and chaperone therapy for disease-susceptible mutations (**Figure 1(E)**).

### 3.1. Enzyme Treatments

Enzyme replacement therapy (ERT)

ERT consists of the administration of agalsidase alfa and agalsidase beta, which are recombinant enzymes administered every 15 days for life, which can eliminate excessive Gb3 storage deposits. This reduction in Gb3 deposits, with a consequent decrease in inflammation, results in a decrease in LVH, in addition to serving as an aid in increasing myocardial function in patients with FD in the early stages. However, the results observed in patients with more than two affected regions of the LV did not improve the function of this chamber or reduce LVH [34].

a) $\alpha$-Pegunigalsidase

It is a pegylated form of $\alpha$-Gal, which has shown in preclinical studies a greatly increased vascular half-life (53 - 121 hours) compared to the current traditional ERT (2 h), in addition to better uptake by the kidneys and heart. However, this topic is still under investigation [35].

### 3.2. Gene Therapy

It consists of the administration of genes mediated by adeno-associated viruses to improve enzyme levels. Currently, the use of mRNA with nanoparticles, without the need for viral vectors, has been studied to look for an increase in $\alpha$-Gal levels. Recently, it was possible to formulate mRNA with lipid nanoparticles, which led to greater production of $\alpha$-Gal, with the consequent elimination of Gb3 deposits [36].

Treatments without enzyme replacement

c) 6,3 Chaperones

Chaperones constitute a therapeutic approach based on the inhibition of glucosylceramide synthase, which reduces the Gb3 levels. The most recently approved and used chaperone is migalastat, which can enhance the series of susceptible mutations that occur in *α*-gal A, in addition to promoting better lysosomal activity [37].

d) Lucerastat

Chaperone, used in the therapeutic approach to FD, fulfills its function as an inhibitor by not allowing the accumulation of Gb3 deposits, which leads to a reduction of ceramide converted into glycosphingolipid. The efficacy and biosafety of FD are still under evaluation [38].

## 4. Discussion

Excessive accumulation of glycosphingolipids in multiple organs, with cardiovascular compromise, contributes to disease progression and mortality [3]. Recent research has made strides in understanding the pathophysiology of FD and in developing therapeutic interventions aimed at managing its cardiovascular manifestations.

The understanding of FD has evolved significantly, with advancements in diagnostic techniques such as echocardiography and CMRI enabling more accurate detection and monitoring of cardiac involvement [26].

A multimodal approach is extremely important for the diagnosis of FD. It is common for patients to lead a normal life without symptoms, and for the first manifestation of the disease to be a major cerebrovascular event.

Early detection of subclinical cardiac involvement, as allowed by echocardiographic assessment, may become a critical element in clinical decision-making, especially in young patients [38]. It is highlighted that, despite having the diagnostic tools available, FD was not initially suspected, although the transthoracic echocardiogram and CMRI showed typical data of the disease, with marked LVH, diastolic dysfunction, normal systolic function with preserved LVEF and LV strain with a type 3 pattern, and LGE with a non-ischemic pattern, which suggests that FD is underdiagnosed, and that it is necessary to have a deeper understanding of this disease [39]. Additionally, the implementation of enzyme replacement therapy (ERT) and emerging treatments like gene therapy and chaperone therapy have shown promise in reducing Gb3 deposits and improving clinical outcomes.

FD can present in classic and late phenotypes, with cardiac manifestations being predominant, particularly in the late-onset phenotype. CMR imaging is the imaging technique of choice, and echocardiography with strain imaging is an excellent complement. Further studies are needed to propose prognostic markers for FD, to guide the initiation of therapy, and to monitor its progression [23]. Common cardiac findings include LVH, heart failure, arrhythmias, and sudden

cardiac death underscoring the importance of early diagnosis and intervention. Notably, speckle tracking echocardiography and T1/T2 mapping on CMRI offer greater sensitivity for detecting early myocardial changes and inflammation, guiding treatment decisions and prognostication. It is imperative that the patient starts with specific therapy since it has been found to decrease the progression of the disease [40].

The current treatment modalities for FD primarily revolve around ERT, which aims to reduce Gb3 accumulation and alleviate cardiac symptoms. However, emerging therapies, such as gene therapy and chaperone therapy, hold promise for enhancing treatment efficacy and addressing disease progression, particularly in advanced stages. Future research should focus on elucidating the role of myocardial inflammation in FD pathogenesis and developing targeted interventions to mitigate its impact on disease progression [38].

This comprehensive analysis underscores the importance of multidisciplinary approaches in managing FD, with a particular emphasis on cardiovascular involvement. Future research directions could include investigating novel biomarkers for the early detection of cardiac complications, refining imaging techniques to assess treatment response, and exploring personalized treatment strategies based on genetic profiling and disease phenotype. Additionally, collaborative efforts between clinicians, researchers, and pharmaceutical companies are essential for advancing therapeutic innovations and improving outcomes in individuals with FD.

## 5. Conclusion

FD continues to be a topic of discussion in cardiology, due to the many unknowns that still exist regarding its diagnostic and therapeutic approach. The important role played by echocardiography and MRI as the main noninvasive imaging techniques, which could lead to an early diagnosis of FD and better follow-up, should not be underestimated. Currently, the understanding of cardiac involvement and involvement of FD has made significant advances, which have allowed the implementation of new treatments, although sadly, they are still not accessible to our population.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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