Review Article

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2023;21:8-17
https://doi.org/10.5049/EBP.2023.21.1.8

Management of Hypertension in Fabry Disease

Su Hyun Kim[1], Soo Jeong Choi[2]

[1]*Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Republic of Korea;*
[2]*Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea*

Received: March 31, 2023
Revised: May 5, 2023
Accepted: May 11, 2023
Corresponding Author: Soo Jeong Choi, MD, PhD
Division of Nephrology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, 170 Jomaru-ro, Bucheon 14584, Korea
Tel: +82-32-621-5169; Fax: +82-32-621-5016
E-mail: crystal@schmc.ac.kr

Fabry disease (FD), a rare X-linked lysosomal storage disorder that depletes alpha-galactosidase A (α-GalA), is caused by mutations in the GLA gene. Diminished α-GalA enzyme activity results in the accumulation of Gb3 and lyso-Gb3. The pathophysiology of hypertension in FD is complex and unclear. The storage of Gb3 in arterial endothelial cells and smooth muscle cells is known to produce vascular injury by increasing oxidative stress and inflammatory cytokines as a primary pathophysiological mechanism. In addition, Fabry nephropathy developed, resulting in a decrease in kidney function and contributing to hypertension.

The prevalence of hypertension in patients with FD was between 28.4% and 56%, whereas hypertension in patients with chronic kidney disease ranged between 33% and 79%. A study using 24-hour ambulatory blood pressure monitoring (ABPM) to measure blood pressure (BP) indicated a high prevalence of uncontrolled hypertension in FD. Thus, 24-hour ABPM ought to be considered for FD hypertension assessments.

Appropriate treatment of hypertension is believed to reduce mortality in patients with FD caused by kidney disease, cardiovascular disease, and cerebrovascular disease because hypertension significantly impacts organ damage. Up to 70% of FD patients have been reported to have kidney involvement, and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers prescribed for proteinuria are recommended as first-line therapy with antihypertensive drugs. In conclusion, hypertension should be controlled appropriately, given the different morbidity and mortality caused by significant organ involvement in FD patients.

Key Words: Fabry disease, Hypertension, Enzyme replacement therapy, Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers

INTRODUCTION

Fabry disease (FD) is a rare multisystemic and X-linked lysosomal storage disease. It is caused by mutations in the galactosidase alpha (GLA) gene, resulting in a deficiency of alpha-galactosidase A (α-GalA) enzyme function[1]. The reduced or absent α-GalA activity causes the progressive accumulation of glycosphingolipids, especially globotriaosylceramide (Gb3; also abbreviated as GL3) and the deacylated Gb3 (globotriaosylsphingosine [lyso-Gb3, also lyso-GL3]) in various cell types and organs, including the kidney, heart, skin, blood vessels, peripheral nerves, and central nervous system. The prevalence of FD ranges between 1:40,000 and 1:117,000[2-4], and the clinical symptoms are nonspecific and highly variable.

FD can be classified into two phenotypes: "classic" and "later-onset, also called non-classic." In the classic phenotype, affected males have a total, or almost total, absence of α-GalA activity, and the symptoms typically appear in childhood or adolescence[1]. These symptoms include peripheral neuropathic pain, hypohidrosis, cutaneous angiokeratomas, lenticular and corneal verticillata, gastrointestinal symptoms including abdominal pain and diarrhea, micro-

albuminuria, and proteinuria. As patients age, they may develop serious complications, such as chronic kidney disease, cardiomyopathy, arrhythmias, and cerebrovascular diseases, which can lead to severe morbidity and higher mortality[5-7].

Later-onset or non-classic phenotypes of Fabry patients have variable levels of residual α-GalA activity and heterogeneity in clinical presentations. Therefore, the onset of clinical symptoms is typically between the fourth and sixth decades of life; however, they may manifest in childhood with very different symptoms than the classic phenotype. They are also milder than in the case of the classic phenotype. They are frequently limited to a single organ (usually the heart or kidney)[8,9]. Adult-onset cardiac (cardiomegaly, left ventricular hypertrophy, cardiomyopathy, hypertrophic cardiomyopathy, and myocardial infarction) and renal (end-stage kidney disease) variants are more prevalent[10-12].

Similarly to other X-linked genetic disorders, hemizygous males display more severe clinical symptoms than females. In females, X-linked gene expression is mosaic due to X-chromosome inactivation, which involves the random transcriptional silencing of one X-chromosome in each cell[1]. Consequently, based on penetrance and expression, females can exhibit various symptoms ranging from mild to severe.

The primary pathophysiological mechanism of FD is the storage of Gb3 in lysosomes, which causes cellular dysfunction by inhibiting autophagy and initiating apoptosis[13]. Eliminating accumulated Gb3 using enzyme replacement therapy (ERT) was anticipated to prevent disease progression and alleviate organ damage. Despite ERT treatment, advanced FD showed progressive major organ damage. It may be related to a secondary pathway via increased oxidative stress and induce an immunological response by activating the renin-angiotensin system (RAS) through the storage of lyso-Gb3.

Since it is generally accepted that FD is associated with a low prevalence of hypertension, very few studies have been conducted on it. On the other hand, due to the recent publication of studies on hypertension, there is a growing awareness of the significance of treating hypertension. Thus, we will review the prevalence of hypertension in FD patients, its pathophysiological mechanism, the impact of hypertension on organ damage, and therapies through a review of the literature.

Blood Pressure in Fabry Disease

Patients with FD are known to have significantly lower blood pressure (BP) than the general population[14], despite the high prevalence of heart, kidney, and nervous system diseases associated with high BP. The most plausible explanation is autonomic dysfunction, which includes impaired sweating, reduced saliva and tear production, altered gastrointestinal motility, arrhythmia, and orthostatic hypotension[15,16].

Several factors have been proposed as mechanisms of autonomic dysfunction. First, there is evidence of accumulation of glycosphingolipids and lipid-stained inclusions in central autonomic nuclei and peripheral nerves[17]. And somatic epidermal and dermal autonomic nerve fiber reductions were observed in skin biopsy[18]. FD vasculopathy, including smooth muscle cell hypertrophy with stored glycolipid, also affects autonomic dysfunction by constricting small neural blood vessels[19]. Baroreflex-mediated vasoconstriction due to the dysfunction of sympathetic vasomotor fibers in patients with FD is another known mechanism, as reported by Hilz et al.[20]. In addition, an insufficient increase in heart rate despite physical activity causes exercise intolerance and orthostatic hypotension in advanced stages[21].

Considering these autonomic dysfunctions, it is controversial whether the definition of hypertension in patients with FD can be used for the general population. The autonomic nervous system primarily regulates BP variability[14]. The classification of BP and the definition of hypertension is unchanged from previous European guidelines and is defined as an office systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg, which is equivalent to a 24-h ambulatory BP monitoring (ABPM) average of ≥130/80 mmHg, or a home BP monitoring average ≥135/85 mmHg[22]. Considering the characteristics of low BP in patients with FD, it has been reported that even slightly elevated SBP can be associated with organ damage even if BP does not meet the criteria for hypertension[23]. BP variability was higher in FD patients compared with controls, while there was a decrease in heart rate variability and more non-dipper in FD[14].

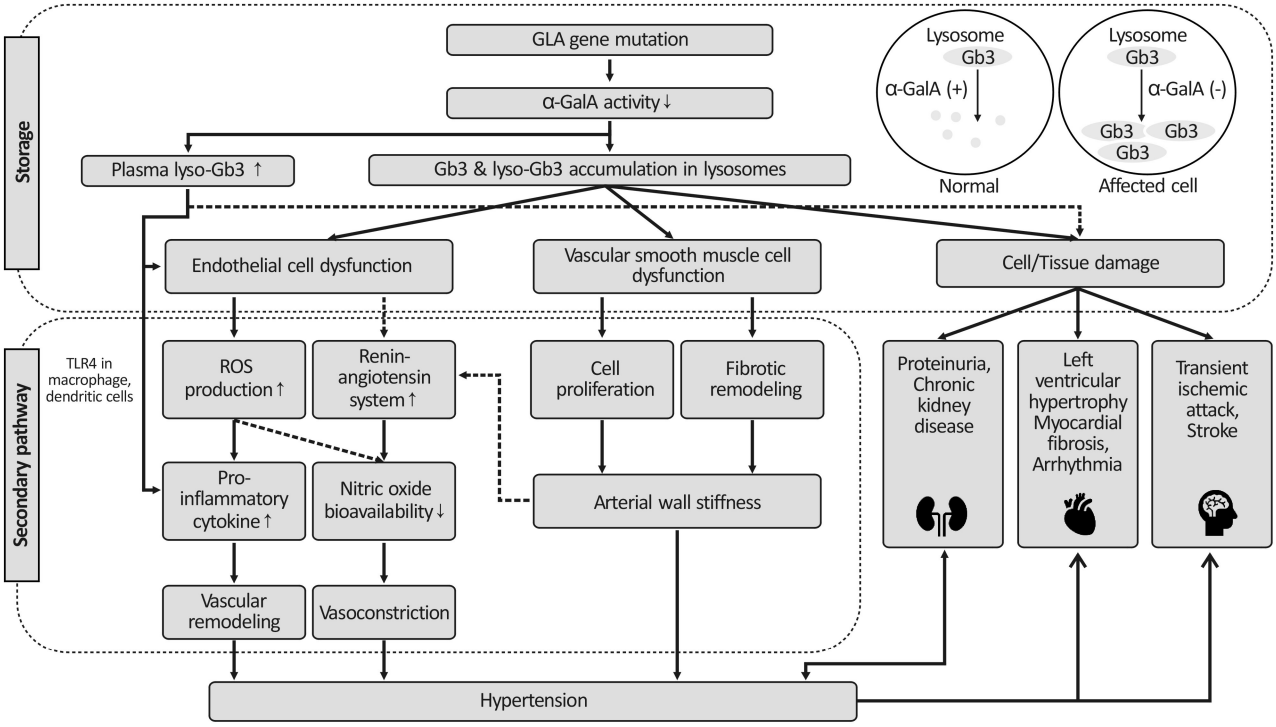

Fig. 1. The proposed pathophysiology of hypertension in Fabry disease. Mutations in the GLA gene reduced alpha-galactosidase A (α-GalA) activity, resulting in the progressive accumulation of Gb3 and lyso-Gb3 in plasma, endothelial cells, and vascular smooth muscle cells, which damages major organ damage. The cellular dysfunction produced by the storage of Gb3 in the lysosome leads to secondary injury, including immunological response through increased reactive oxygen species (ROS) and renin-angiotensin system activation. Chronic kidney disease resulting from FD nephropathy contributes to the development of hypertension. The solid line is a hypothesis based on clinical trials or basic research on Fabry disease. In contrast, the dotted lines reflect an assumed theory based on the mechanism of essential hypertension.

In a recent study by Rossi et al. on outpatient monitoring, 18.8% of 31 patients with FD had increased BP, and three had masked hypertension[24].

Pathophysiology of Hypertension

The pathophysiological mechanisms underlying hypertension in FD are poorly understood due to the limited number of clinical and basic investigations on the mechanism of hypertension in FD. The accumulation of Gb3 in arterial endothelial cells and smooth muscle cells is considered the key pathophysiologic mechanism for inducing hypertension-related vascular injury (Fig. 1)[19,25].

Essential hypertension is associated with an elevation of reactive oxygen species (ROS), which induce pro-inflammatory cytokines and vascular remodeling[26]. Gb3 loading into endothelial cells causes intracellular ROS and increases the expression of cell adhesion molecules[27]. Increased ROS production eventually triggers an increase in pro-inflammatory cytokines, resulting in vascular remodeling. In a study targeting FD cardiomyopathy, interleukin-6 (IL-6), interleukin-1 β (IL-1β), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1), which is the pro-inflammatory cytokine, were significantly higher than those of the control group, suggesting that pro-inflammatory cytokines affect hypertension in FD[28].

FD patients may have a potential relationship between the RAS system and hypertension, as the activation of angiotensin II can reduce the activity of endothelial nitric oxide synthase (eNOS) activity, leading to vasoconstriction and elevated BP, a mechanism also observed in the general population[29]. Additionally, research by Fujii et al. indicates that Gb3 and angiotensin-converting enzyme (ACE) are expressed in the same location in the proximal tubules, while Batista

et al. found that α-GalA infusion inhibits ACE activity, leading to a temporary reduction in BP in Fabry patients after ERT[30,31]. However, the effects were compensated with upregulated ACE activity and increased plasma angiotensin II two weeks later. Bothou et al. also found a positive correlation between elevated renin and lyso-Gb3 levels in men with FD, while Shu et al. demonstrated that aortic endothelial cells lacking α-GalA had decreased eNOS activity and nitric oxide availability[32,33]. While these findings suggest a potential role of the RAS system in hypertension development in FD patients, further research is needed to confirm this relationship.

In addition, Gb3 is known to stimulate cell proliferation and fibrosis in smooth muscle cells, leading to inflammation and elevated BP. Storage of lyso-Gb3 within the medial layer of the arteries may also promote smooth muscle cell proliferation, with the fibrotic remodeling of the arterial wall leading to arterial wall stiffness[34]. Aerts et al. report that lyso-Gb3 dramatically increased the plasma of affected FD patients and tissues of FD mice and induced smooth muscle cell proliferation in vitro[34]. Barbey et al. showed that plasma from FD could stimulate the proliferation of vascular smooth muscle cells and cardiomyocytes[35]. The resulting shear stress may increase the expression of angiotensin I and II receptors in endothelial cells, increasing ROS, and decreasing NO synthesis[19]. These factors may initiate an inflammatory cascade with pro-thrombotic and pro-inflammatory effects on endothelial cells and vascular smooth muscle cells[19,36].

Pinto et al. reported that an immune response causes hypertension in patients with FD, and innate immunity also plays a major role[37]. The innate immune system recognizes danger signals through pattern recognition receptors, such as toll-like receptor 4 (TLR4), expressed primarily on the surface of macrophages and dendritic cells. Glycolipids such as lyso-Gb3 can bind to TLR4 in FD, which in turn activates the NF-κB pathway to release pro-inflammatory cytokines and trigger systemic and local inflammatory responses[38,39].

As FD nephropathy advances, CKD occurs, contributing to hypertension development. Kidney involvement is already known to be extremely prevalent in FD, and Gb3 deposition in the kidney is a primary cause[40]. In addition, high BP itself contributes to kidney damage; hence, high BP and kidney damage are tightly linked. In general, untreated patients present three clinical stages of FD nephropathy, depending on their age. In the first stage (infancy and adolescence), there is glomerular hyperfiltration. In the second (adult) stage, it is kidney-related with proteinuria and lipiduria, and in the third stage, severe kidney and cardiovascular complications develop, resulting in hypertension[41].

Hypertension is a progressive disease whose prevalence increases with advancing age. It is also known that the prevalence of hypertension increases with age in FD. In particular, the prevalence of kidney and cardiovascular diseases, which are highly related to hypertension, increases with age, so this effect is thought to have an impact[42,43].

Prevalence of Hypertension in Fabry Disease

According to a meta-analysis of the general European population, the prevalence of hypertension was 44.2%[44]. In a study of patients in the United States, the prevalence of hypertension in patients with chronic kidney disease was between 80 and 85 percent[45]. The prevalence of hypertension in patients with FD has been observed to range between 28% and 63.5% (Table 1)[14,24,40,41,46-51]. In the study by Lenders, hypertension was as high as 63.5%, which is attributed to the fact that the average age was older than in earlier studies, and the group with albuminuria reached 75.0%[50].

The majority of the research that reported the prevalence of hypertension was based on cross-sectional studies, and because of this, it was not able to adequately estimate the prevalence of hypertension using information such as medical history and the use of antihypertensive medicines. Two studies found that when the BP of FD patients was measured using ABPM, the prevalence of hypertension was 31-40%[14,24]. Considering that 5% to 41% of the patients had a glomerular filtration rate of less than 60, including other cross-sectional studies, hypertension in patients with FD was lower than in the general population.

Conversely, there is evidence that patients with FD have a high prevalence of uncontrolled hypertension. Kleinert et al. reported that among 391 patients with FD, 57% of males and 47% of females had uncontrolled hypertension when hypertension was defined as SBP ≥130 mmHg and

Table 1. Prevalence of hypertension in Fabry patients

Author, year	Region	N	Male (%)	Age (year)	Diagnosis of HTN	eGFR	eGFR<60, n (%)	HTN, n (%)	HTN in CKD, n (%)	Kidney involvement, %	CNS involvement, %	Cardiac involvement, %	ERT/Chaperon therapy, %	ACEi/ARBs, %
Dincer, 2022	Turkey	30	53.3	38.1±13.4		91.7±40.8	9 (30%)	12 (40%)	5 (55.6%)	71	35.4	32.3	96.8	35.5
Ferrari, 2021	Argentina	93	44.0	32±16.6	History of HTN	-	38 (41%)	26 (28%)	-	41	-	47	100	-
Rossi, 2021	Europe	32	25.0	50.3±12.4	SBP ≥130 or DBP≥80 mmHg vis ABPM	-	6 (19%)	10 (31%)	2 (33%)	32.3	65.6	90.6	59.4	21.9
Lenders, 2020	Germany	59	53.0	49±13	History of HTN	-	1 (5%)	33 (63.5%)	-	70.8	-	68	57.6	72.1
Wang, 2020	Taiwan	22	72.7	47 (32.8–56.3]	History of HTN	83.6 (59.8–112.2)	2 (9.1%)	9 (40.9%)	-	-	-	24.7	-	-
Lidove, 2016 (FOS)	Global	2,044	56.0	≥18	History of HTN	-	-	599 (29%)	-	48.9	19.7	66.3	67.2	35.6
Schiffmann, 2009	Global	395	61.0	41.0 (5.0–77.1)	History of HTN	-	77 (19%)	221 (56%)	61 (79%)	26.3	17	58.7	100	16.7
Ortiz, 2008	Global	1,262	46.0	-	SBP ≥130 or DBP≥80 mmHg vis office BP	81/82 for male and female	255 (20%)	554 (44%)	-	-	-	-	-	-
Kleinert, 2006 (FOS)	Global	391	54.0	40 (24, 58)	SBP ≥130 or DBP≥80 mmHg vis office BP	79 (53, 109)	104 (27%)	205 (52.4%)	70 (67%)	-	-	-	-	24.9
Branton, 2002	USA	105	100.0	38±11	History of HTN	-	-	31 (30%)	-	74.3	-	-	-	19

ABPM, Ambulatory blood pressure monitoring; ACEi, Angiotensin-Converting Enzyme Inhibitors; ARBs, Angiotensin II receptor blockers; FOS, Fabry Outcome Survey registry; HTN, hypertension; CKD, chronic kidney disease

DBP ≥90 mmHg[51]. Rossi et al. demonstrated the importance of ABPM by reporting that hypertension was detected in three (9.4%) patients by normal clinic measurements, while increased BP was found in six (18.8%) patients by ambulatory monitoring, which revealed three cases of masked hypertension[24].

There may be heterogeneity in the reported data due to differences in study group age and kidney function at baseline. Hypertension prevalence increases with age in Fabry Outcome Survey (57.7% aged ≥75 years; 48.2% aged 65-74; 41.9% aged 50-64; 21.8% aged 18-49)[47]. According to Branton and colleagues, hypertension was not a prominent feature in this population, often not manifesting until patients experienced a decline in kidney function, and they proposed that hypertension is more likely to be essential or secondary to pre-existing kidney disease[46].

The incidence of hypertension in patients with FD often increases with decreased kidney function. Patients with a glomerular filtration rate of less than 60 mL/min/1.73 m^2 had higher BP, according to a study by Ortiz et al.[40]. Schiffman et al. also reported that approximately 80% of patients with CKD had hypertension, whereas about 50% had a glomerular filtration rate of ≥60 mL/min/1.73 m^2 [41]. Dincer et al. reported the 24-hour BP determined by ABPM was significantly different between GFR <60 ml/min and greater than 60, while the proportions of patients taking antihypertensive drugs were similar[14].

Many studies show gender does affect hypertension. Ortiz et al. reported no difference between genders in the eGFR <60 and ≥60 groups[40]. In the group under 40 years old, however, there was a substantially higher frequency of hypertension among males (51%) than females (35%; p= 0.0003) with CKD stages 1 or 2[40]. These results might suggest organ involvement is associated with hypertension rather than gender.

Considering that the BP of FD patients is lower than that of the general population, the prevalence of hypertension is likely to be higher than estimated; therefore, additional research is necessary. In addition, since most studies have diagnosed hypertension by taking a patient's medical history and prescribing medication, tests such as ABPM should be considered to prevent major organ damage and active treatment of hypertension in patients with FD.

Hypertension and Major Organ Damage

The major consequences of hypertension are myocardial infarction, heart failure, stroke, and kidney failure. In the general population, for every 20 mmHg increase in SBP or 10 mmHg increase in DBP, the risk of cardiovascular disease doubles[52].

Hypertension contributes to the disease burden of FD,

just as it contributes to the disease burden of many other conditions in the general population. Due to the high prevalence of kidney, cardiac, and neurological diseases in FD, hypertension has detrimental effects on disease progression and prognosis despite the low prevalence of hypertension in patients with FD compared to the general population[53].

Fabry nephropathy presents with a wide range of disease severity in males and females, proteinuria is typically a manifestation of podocyte injury, and urinary protein excretion is strongly associated with Fabry nephropathy progression[40,54]. A high prevalence of uncontrolled BP was reported in patients with FD and deteriorating CKD in the Fabry Outcome Survey Registry and the Fabry Registry[40,51]. Otiz et al. found SBP was higher with lower eGFR in Fabry patients[40]. Proteinuria in kidney disease is generally recognized as a risk factor for disease progression[40,55]. These findings suggest that hypertension may contribute to the decline of kidney function.

There is also evidence of an association between hypertension and cardiovascular disease in FD. Cardiovascular disease was the most common cause of death in both genders, accounting for 40% of men and 41.7% of women[5]. Linhart et al. evaluated the cause of death on 113 affected relatives of 714 patients with FD[56]. Cardiovascular mortality rate was most frequent in 41 female, while that was the second cause in 72 men. In a study by Patel et al., hypertension increased the odds of a cardiovascular event (myocardial infarction, heart failure, or heart-related death) by 7.8 in men and 4.5 in women[57].

Hypertension has been considered the most crucial risk factor for cerebrovascular disease (CVD) in FD[58]. At the Fabry Registry, patients with CVD were more likely than FD patients without CVD to report a history of hypertension, 52.9% versus 20.5%, respectively[59]. A greater proportion of female stroke patients reported a history of hypertension than male stroke patients (32 of 52, 61.5%).

Management of Hypertension

As described above, as few as 30% to as many as 50% or more of FD patients are accompanied by hypertension [14,24,46-49]. Appropriate treatment of such hypertension contributes to the reduction of mortality due to kidney, cardiovascular, and cerebrovascular diseases in FD patients and, consequently, may positively affect the disease progression and prognosis of FD, so active hypertension treatment is recommended[40,51].

The European Society of Hypertension-European Society of Cardiology guidelines suggest that a target BP in patients with FD with proteinuria >1 g/day should be less than 125/75 mmHg, whereas a target BP in patients with FD with proteinuria of 0.25-1 g/day should be 130/80 mmHg[60,61]. In addition to ERT, the current treatment guidelines published by Eng et al. emphasize the importance of managing hypertension in patients with kidney disease[62].

When treating hypertension in patients with FD, it may be beneficial to consider medications that offer organ-protective effects, such as for the kidney, heart, and brain. Medications for hypertension in Fabry patients may include angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), calcium channel blockers (CCBs), or beta-blockers. Additionally, sodium-glucose cotransporter 2 (SGLT2) inhibitors, which have recently emerged as a potential new antihypertensive drug, can also be considered.

ACEi/ARBs are the primary medications prescribed for hypertensive patients with FD. This is because proteinuria is very common in patients with FD, and it is the first-line treatment for proteinuria. Management of proteinuria is a critical feature in preserving kidney function in patients with FD. A consistent antiproteinuric therapy with ACEi or ARBs was shown to decrease the progression of kidney disease in FD[63,64]. Table 1 shows that ACEi/ARBs were used (16.7-71%) for organ damage in patients with FD.

Monitoring BP while using ACEi/ARBs is essential because sudden hypotension can impair kidney function. Although patients with hypertension were not targeted, Muntze's study reported that kidney function deteriorated after using ACEi/ARBs[65]. They said that migalastat was used as a treatment drug, and the left ventricular mass index significantly decreased in 14 patients while eGFR significantly deteriorated. The authors observed a significant correlation between the initiation of ACEi and SBP drop below 120, leading to a higher risk of kidney function deterioration. Hence, when BP falls below SBP 120 during the initiation of antihypertensive medications like ACEi, it is crucial to closely monitor BP to prevent any potential kidney function decline.

CCBs may be considered as a potential treatment option for hypertension in FD, but evidence for their use is lacking[66]. However, chest pain is a common symptom in FD patients, with up to 60% of hemizygous males and heterozygous females experiencing it[67]. For treating angina and left ventricular outflow tract obstruction, CCBs like verapamil and diltiazem should be considered[68].

Beta-blockers with high cardiac selectivity are recommended for patients with angina pectoris, myocardial infarction, or tachycardia[69,70]. But when prescribing beta-blockers to patients with FD, caution is necessary due to the increased risk of bradyarrhythmias and chronotropic incompetence[71]. A high prevalence of symptomatic heart failure (47 out of 116 patients, 69 classic types and 47 late-onset) was reported in FD patients by Rob et al., with beta-blockers being the most frequently used medication (51%), followed by ACEi (43%), diuretics (28%), ARBs (15%), and MRAs (8.5%)[72].

Steroidal and non-steroidal MRAs are recommended for their kidney protective effects, which include reducing proteinuria, as well as their cardioprotective effects in patients with heart failure[69,73,74]. However, it should be noted that there are risks of hyperkalemia or acute kidney injury, so caution must be taken when administering these medications as part of hypertension treatment.

SGLT2 inhibitors have demonstrated the potential to lower BP, suggesting their use as new antihypertensive drugs[75]. Even in patients with FD, SGLT2 inhibitors, similar to RAS blockade, may provide optimal kidney protection and control of systemic and intrarenal BP[76]. While recent findings suggest no risk of acute kidney injury associated with SGLT2 inhibitors, caution should still be exercised when using these drugs in patients with altered kidney function due to volume depletion[77]. Although there are no direct study results on the effect of SGLT2 inhibitors on FD, clinical studies are scheduled to be conducted and results are anticipated[78].

Since a high-sodium diet can reduce the effectiveness of ACEi/ARBs[79] and is associated with an increased risk of progression to end-stage kidney disease in patients with proteinuria[80], a low-sodium diet is strongly recommended for FD patients with proteinuria[81].

The FD-specific current treatments are ERT and chaperone therapy, which reduce intracellular Gb3 accumulation. ERT involves exogenous supplementation of α-GalA enzymes such as Fabrazyme and Replagal. Migalastat hydrochloride is an oral pharmacological chaperone that corrects the misfolded endogenous α-GalA and promotes the transport of α-GalA into lysosomes. Other future therapies, such as matrix reduction therapy, mRNA-based therapy, and gene therapy, are under development[81].

Two studies found that ERT treatment improved hypertension and decreased proteinuria[82,83]. However, it is difficult to fully explain the effect of ERT alone, given that the patients who participated in these studies were also getting ACEi or ARBs medication. ACEi and ARBs are routinely used to protect the kidneys in FD. There are reports that ERT can reduce inflammation by regulating the immune system. FD leads to the activation of the pro-inflammatory pathway associated with hypertension. ERT may modulate the immune system to reduce the level of inflammation.

In conclusion, the improved treatment of hypertension has probably contributed to the decline in kidney and cardiovascular disease-related mortality in FD patients. All Fabry patients should have adequate control over their BP. As indicated previously, because of uncontrolled hypertension, 24-hour BP measurements and oral medications such as ACEi/ARBs should be considered while monitoring BP.

Conflict of Interest

The authors have no conflicts of interest to declare

REFERENCES

1. Germain DP: Fabry disease. Orphanet J Rare Dis 2010;5:30.
2. Desnick RJ, Brady R, Barranger J, et al.: Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med 2003;138(4):338-46.
3. Linthorst GE, Hollak CE, Korevaar JC, Van Manen JG, Aerts JM, Boeschoten EW: Alpha-Galactosidase A deficiency in Dutch patients on dialysis: a critical appraisal of screening for Fabry disease. Nephrol Dial Transplant 2003;18(8):1581-4.
4. Gibas AL, Klatt R, Johnson J, Clarke JT, Katz J: Disease rarity, carrier status, and gender: a triple disadvantage for women

with Fabry disease. J Genet Couns 2008;17(6):528-37.
5. Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P: Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. Genet Med 2009;11(11):790-6.
6. Nowak A, Mechtler T, Kasper DC, Desnick RJ: Correlation of Lyso-Gb3 levels in dried blood spots and sera from patients with classic and Later-Onset Fabry disease. Mol Genet Metab 2017;121(4):320-4.
7. Hoffmann B: Fabry disease: recent advances in pathology, diagnosis, treatment and monitoring. Orphanet J Rare Dis 2009;4:21.
8. Mehta A, Ricci R, Widmer U, et al.: Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest 2004;34(3):236-42.
9. Yuasa T, Takenaka T, Higuchi K, et al.: Fabry disease. J Echocardiogr 2017;15(4):151-7.
10. Jaurretche S, Antongiovanni N, Perretta F: Fabry nephropathy. Role of nephrologist and clinical variables associated with the diagnosis. Nefrología (English Edition) 2019;39(3):294-300.
11. Choi JH, Lee BH, Heo SH, et al.: Clinical characteristics and mutation spectrum of GLA in Korean patients with Fabry disease by a nationwide survey: Underdiagnosis of late-onset phenotype. Medicine (Baltimore) 2017;96(29):e7387.
12. Doheny D, Srinivasan R, Pagant S, Chen B, Yasuda M, Desnick RJ: Fabry Disease: prevalence of affected males and heterozygotes with pathogenic GLA mutations identified by screening renal, cardiac and stroke clinics, 1995-2017. J Med Genet 2018;55(4):261-8.
13. Tuttolomondo A, Simonetta I, Riolo R, et al.: Pathogenesis and Molecular Mechanisms of Anderson-Fabry Disease and Possible New Molecular Addressed Therapeutic Strategies. Int J Mol Sci 2021;22(18).
14. Dincer MT, Ozcan SG, Ikitimur B, et al.: Blood Pressure Variability in Fabry Disease Patients. Nephron 2022;146(4):343-50.
15. Cable WJ, Kolodny EH, Adams RD. Fabry disease: impaired autonomic function. Neurology 1982;32(5):498-502.
16. Biegstraaten M, van Schaik IN, Wieling W, Wijburg FA, Hollak CE: Autonomic neuropathy in Fabry disease: a prospective study using the Autonomic Symptom Profile and cardiovascular autonomic function tests. BMC Neurol 2010; 10:38.
17. Kaye EM, Kolodny EH, Logigian EL, Ullman MD: Nervous system involvement in Fabry's disease: clinicopathological and biochemical correlation. Ann Neurol 1988;23(5):505-9.
18. Liguori R, Di Stasi V, Bugiardini E, et al.: Small fiber neuropathy in female patients with fabry disease. Muscle Nerve 2010;41(3):409-12.
19. Rombach SM, Twickler TB, Aerts JM, Linthorst GE, Wijburg FA, Hollak CE: Vasculopathy in patients with Fabry disease: current controversies and research directions. Mol Genet Metab 2010;99(2):99-108.
20. Hilz MJ, Marthol H, Schwab S, Kolodny EH, Brys M, Stemper B: Enzyme replacement therapy improves cardiovascular responses to orthostatic challenge in Fabry patients. J Hypertens 2010;28(7):1438-48.
21. Burlina AP, Sims KB, Politei JM, et al.: Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. BMC Neurol 2011;11:61.
22. Williams B, Mancia G, Spiering W, et al.: 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Blood Press 2018;27(6):314-40.
23. Fervenza FC, Torra R, Warnock DG: Safety and efficacy of enzyme replacement therapy in the nephropathy of Fabry disease. Biologics 2008;2(4):823-43.
24. Rossi F, Svarstad E, Elsaid H, et al.: Elevated Ambulatory Blood Pressure Measurements are Associated with a Progressive Form of Fabry Disease. High Blood Press Cardiovasc Prev 2021;28(3):309-19.
25. DeGraba T, Azhar S, Dignat-George F, et al.: Profile of endothelial and leukocyte activation in Fabry patients. Ann Neurol 2000;47(2):229-33.
26. Lassegue B, Griendling KK: Reactive oxygen species in hypertension; An update. Am J Hypertens 2004;17(9):852-60.
27. Shen JS, Meng XL, Moore DF, et al.: Globotriaosylceramide induces oxidative stress and up-regulates cell adhesion molecule expression in Fabry disease endothelial cells. Mol Genet Metab 2008;95(3):163-8.
28. Chen KH, Chien Y, Wang KL, et al. Evaluation of Proinflammatory Prognostic Biomarkers for Fabry Cardiomyopathy With Enzyme Replacement Therapy. Can J Cardiol 2016; 32(10):1221 e1-e9.
29. Ding J, Yu M, Jiang J, et al.: Angiotensin II Decreases Endothelial Nitric Oxide Synthase Phosphorylation via AT(1)R Nox/ROS/PP2A Pathway. Front Physiol 2020;11:566410.
30. Fujii Y, Numata S, Nakamura Y, et al.: Murine glycosyltransferases responsible for the expression of globo-series glycolipids: cDNA structures, mRNA expression, and distribution of their products. Glycobiology 2005;15(12):1257-67.
31. Batista EC, Carvalho LR, Casarini DE, et al.: ACE activity is modulated by the enzyme alpha-galactosidase A. J Mol Med (Berl) 2011;89(1):65-74.
32. Bothou C, Beuschlein F, Nowak A: Endocrine disorders in patients with Fabry disease: insights from a reference cen-

tre prospective study. Endocrine 2022;75(3):728-39.
33. Shu L, Park JL, Byun J, Pennathur S, Kollmeyer J, Shayman JA: Decreased nitric oxide bioavailability in a mouse model of Fabry disease. J Am Soc Nephrol 2009;20(9):1975-85.
34. Aerts JM, Groener JE, Kuiper S, et al.: Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proc Natl Acad Sci USA 2008;105(8):2812-7.
35. Barbey F, Brakch N, Linhart A, et al.: Cardiac and vascular hypertrophy in Fabry disease: evidence for a new mechanism independent of blood pressure and glycosphingolipid deposition. Arterioscler Thromb Vasc Biol 2006;26(4):839-44.
36. Dandona P, Dhindsa S, Ghanim H, Chaudhuri A: Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. J Hum Hypertens 2007;21(1):20-7.
37. Del Pinto R, Ferri C: The role of Immunity in Fabry Disease and Hypertension: A Review of a Novel Common Pathway. High Blood Press Cardiovasc Prev 2020;27(6):539-46.
38. Anders HJ, Banas B, Schlondorff D: Signaling danger: toll-like receptors and their potential roles in kidney disease. J Am Soc Nephrol 2004;15(4):854-67.
39. Sanchez-Nino MD, Carpio D, Sanz AB, Ruiz-Ortega M, Mezzano S, Ortiz A: Lyso-Gb3 activates Notch1 in human podocytes. Hum Mol Genet 2015;24(20):5720-32.
40. Ortiz A, Oliveira JP, Waldek S, et al.: Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy. Nephrol Dial Transplant 2008;23(5):1600-7.
41. Schiffmann R, Warnock DG, Banikazemi M, et al.: Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrol Dial Transplant 2009;24(7):2102-11.
42. Carson AP, Howard G, Burke GL, Shea S, Levitan EB, Muntner P: Ethnic differences in hypertension incidence among middle-aged and older adults: the multi-ethnic study of atherosclerosis. Hypertension 2011;57(6):1101-7.
43. Egan BM, Zhao Y, Axon RN: US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. JAMA 2010;303(20):2043-50.
44. Wolf-Maier K, Cooper RS, Banegas JR, et al.: Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA 2003;289(18):2363-9.
45. Whaley-Connell AT, Sowers JR, Stevens LA, et al.: CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis 2008;51(4 Suppl 2):S13-20.
46. Branton MH, Schiffmann R, Sabnis SG, et al.: Natural history of Fabry renal disease: influence of alpha-galactosidase A activity and genetic mutations on clinical course. Medicine (Baltimore) 2002;81(2):122-38.
47. Lidove O, Barbey F, Niu DM, et al.: Fabry in the older patient: Clinical consequences and possibilities for treatment. Mol Genet Metab 2016;118(4):319-25.
48. Ferrari G, Reisin R, Kisinovsky I, et al.: Major cardiovascular adverse events in Fabry disease patients receiving agalsidase alfa. Medicina (B Aires) 2021;81(2):173-9.
49. Wang WT, Sung SH, Liao JN, Hsu TR, Niu DM, Yu WC: Cardiac manifestations in patients with classical or cardiac subtype of Fabry disease. J Chin Med Assoc 2020;83(9):825-9.
50. Lenders M, Nordbeck P, Kurschat C, et al.: Treatment of Fabry's Disease With Migalastat: Outcome From a Prospective Observational Multicenter Study (FAMOUS). Clin Pharmacol Ther 2020;108(2):326-37.
51. Kleinert J, Dehout F, Schwarting A, et al.: Prevalence of uncontrolled hypertension in patients with Fabry disease. Am J Hypertens 2006;19(8):782-7.
52. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360(9349):1903-13.
53. Krämer J, Bijnens B, Störk S, et al.: Left Ventricular Geometry and Blood Pressure as Predictors of Adverse Progression of Fabry Cardiomyopathy. PLoS One 2015;10(11):e0140627.
54. Wanner C, Oliveira JP, Ortiz A, et al.: Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry. Clin J Am Soc Nephrol 2010;5(12):2220-8.
55. Ruggenenti P, Perna A, Remuzzi G, Investigators GG: Retarding progression of chronic renal disease: the neglected issue of residual proteinuria. Kidney Int 2003;63(6):2254-61.
56. Linhart A, Kampmann C, Zamorano JL, et al.: Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. Eur Heart J 2007;28(10):1228-35.
57. Patel MR, Cecchi F, Cizmarik M, et al.: Cardiovascular events in patients with fabry disease natural history data from the fabry registry. J Am Coll Cardiol 2011;57(9):1093-9.
58. Viana-Baptista M: Stroke and Fabry disease. J Neurol 2012;259(6):1019-28.
59. Sims K, Politei J, Banikazemi M, Lee P: Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: natural history data from the Fabry Registry. Stroke 2009;40(3):788-94.

60. Mancia G, Fagard R, Narkiewicz K, et al.: 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013; 31(7):1281-357.
61. Schieppati A, Remuzzi G: Proteinuria and its consequences in renal disease. Acta Paediatr Suppl 2003;92(443):9-13;discussion 5.
62. Eng CM, Germain DP, Banikazemi M, et al.: Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. Genet Med 2006;8(9):539-48.
63. Warnock DG, Ortiz A, Mauer M, et al.: Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation. Nephrol Dial Transplant 2012;27(3):1042-9.
64. Warnock DG, Thomas CP, Vujkovac B, et al.: Antiproteinuric therapy and Fabry nephropathy: factors associated with preserved kidney function during agalsidase-beta therapy. J Med Genet 2015;52(12):860-6.
65. Muntze J, Gensler D, Maniuc O, et al.: Oral Chaperone Therapy Migalastat for Treating Fabry Disease: Enzymatic Response and Serum Biomarker Changes After 1 Year. Clin Pharmacol Ther 2019;105(5):1224-33.
66. Paim-Marques L, de Oliveira RJ, Appenzeller S. Multidisciplinary Management of Fabry Disease: Current Perspectives. J Multidiscip Healthc 2022;15:485-95.
67. Elliott PM, Kindler H, Shah JS, et al.: Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A. Heart 2006;92(3):357-60.
68. Azevedo O, Cordeiro F, Gago MF, et al.: Fabry Disease and the Heart: A Comprehensive Review. Int J Mol Sci 2021; 22(9).
69. Unger T, Borghi C, Charchar F, et al.: 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension 2020;75(6):1334-57.
70. Williams B, Mancia G, Spiering W, et al.: 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39(33):3021-104.
71. Hagege A, Reant P, Habib G, et al.: Fabry disease in cardiology practice: Literature review and expert point of view. Arch Cardiovasc Dis 2019;112(4):278-87.
72. Rob D, Marek J, Dostalova G, Linhart A: Heart failure in Fabry disease revisited: application of current heart failure guidelines and recommendations. ESC Heart Fail 2022;9(6): 4043-52.
73. Bakris G, Yang YF, Pitt B: Mineralocorticoid Receptor Antagonists for Hypertension Management in Advanced Chronic Kidney Disease: BLOCK-CKD Trial. Hypertension 2020;76(1): 144-9.
74. Heidenreich PA, Bozkurt B, Aguilar D, et al.: 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145(18):e895-e1032.
75. Kario K, Ferdinand KC, Vongpatanasin W: Are SGLT2 Inhibitors New Hypertension Drugs? Circulation 2021;143(18):1750-3.
76. Fioretto P, Zambon A, Rossato M, Busetto L, Vettor R: SGLT2 Inhibitors and the Diabetic Kidney. Diabetes Care 2016;39 Suppl 2:S165-71.
77. Bailey CJ, Day C, Bellary S: Renal Protection with SGLT2 Inhibitors: Effects in Acute and Chronic Kidney Disease. Curr Diab Rep 2022;22(1):39-52.
78. A N: Effects Of Sodium Glucose Cotranspoter 2 Inhibitors On Heart And Kidneys In Fabry Disease Patients. 2023. https://clinicaltrials.gov/ct2/show/NCT05710367 (accessed May, 2023.
79. De'Oliveira JM, Price DA, Fisher ND, et al.: Autonomy of the renin system in type II diabetes mellitus: dietary sodium and renal hemodynamic responses to ACE inhibition. Kidney Int 1997;52(3):771-7.
80. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P: Sodium intake, ACE inhibition, and progression to ESRD. J Am Soc Nephrol 2012;23(1):165-73.
81. Lenders M, Brand E: Fabry Disease: The Current Treatment Landscape. Drugs 2021;81(6):635-45.
82. Whybra C, Miebach E, Mengel E, et al.: A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease. Genet Med 2009;11(6):441-9.
83. Mehta A, Beck M, Elliott P, et al.: Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. Lancet 2009;374(9706):1986-96.