

How Do Physical Activity and Exercise Affect Fabry Disease? Exploring a New Opportunity

Federica Baciga^{a,b} Giacomo Marchi^c Federica Caccia^a Claudia Momentè^a
Pasquale Esposito^{d,e} Filippo Aucella^f Nicola Vitturi^g Laura Pederzoli^h
Meilad Shakkour^a Antonio Granataⁱ Maria Teresa Zicarelli^j
Domenico Girelli^c Michele Andreucci^j Gianni Carraro^k Yuri Battaglia^{a,b}

^aDepartment of Medicine, University of Verona, Verona, Italy; ^bNephrology and Dialysis Unit, Pederzoli Hospital, Garda, Italy; ^cInternal Medicine Unit and MetabERN Health Care Provider, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy; ^dNephrology, Dialysis and Transplantation, Department of Internal Medicine and Medical Specialties (DIMI), University of Genoa, Genoa, Italy; ^eNephrology Clinic, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; ^fNephrology and Dialysis Unit, Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; ^gDepartment of Medicine-DIMED, Division of Metabolic Diseases, University Hospital, Padua, Italy; ^hCardiology Unit, Pederzoli Hospital, Peschiera del Garda, Italy; ⁱNephrology and Dialysis Unit, “Cannizzaro” Emergency Hospital, Catania, Italy; ^jChair of Nephrology, Department of Health Sciences, “Magna Graecia” University, Catanzaro, Italy; ^kNephrology, Dialysis and Transplantation Unit, Department of Medicine, University of Padova, Padua, Italy

Keywords

Fabry disease · Physical exercise · Enzyme replacement therapy · Migalastat · Lysosomal disease · Skeletal muscle · Cardiac · Neurologic · Anemia · Depression · Psychosocial condition

Abstract

Background: Fabry disease (FD) is a multisystem, monogenic, X-linked storage disorder caused by mutations in the *GLA* gene, resulting in reduced alfa-galactosidase A enzyme activity. This effect leads to the accumulation of glycosphingolipids, particularly globotriaosylceramide, in various tissues, including the heart, kidney, vasculature, smooth muscle, and peripheral nervous system. Hemizygous males are usually more severely affected than females, in whom

random inactivation of an X chromosome may lead to variable phenotype. **Summary:** Among the manifestations of FD, exercise intolerance is commonly diagnosed but often underestimated, even though it significantly limits quality of life, especially in young patients. This review primarily discusses the various pathophysiological mechanisms involved in exercise intolerance in FD patients, such as altered muscle composition, compromised cardiopulmonary framework, and peripheral neuropathy. Secondarily, it explores the potential effect of available therapy, including enzyme replacement therapy and chaperone therapy (migalastat), in reducing exercise intolerance while considering the potential impact of physical activity and exercise training as

Federica Baciga and Giacomo Marchi contributed equally to this work.

adjunctive treatments. **Conclusion:** Exercise intolerance has a major impact on the well-being of people with FD. Exercise training can play an important role in addition to drug therapy.

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Introduction

Anderson-Fabry disease (or Fabry Disease, FD [OMIM 301500]) is a rare X-linked lysosomal storage disorder resulting from deficient α -galactosidase A activity [1] due to pathogenic mutations in the *GLA* gene located on the long arm of X chromosome (Xq22.1) that consists of 1,290 base pairs [2]. Deficient α -galactosidase A activity leads to progressive accumulation of globotriaosylceramide (Gb3) and its deacylated form, globotriaosylsphingosine (lysoGb3), within lysosomes of various cells, such as podocytes, cardiomyocytes, and endothelial cells.

There are two forms of the disease: the classic form, which is more severe and precocious (<16 years) and the late-onset form, with later (50–60 years) and milder symptoms [3]. The severity of FD depends on the gender and the degree of enzyme activity. In FD males with the classic form, enzyme activity is either absent or <3% of the normal, while with the late-onset form, it is higher than the classic form, but is lower than expected [4]. Females with FD can also have both forms of the disease. However, heterozygous females have a less predictable disease course due to X-lyonization and variable residual enzyme activity [5, 6]. The type of mutation also influences the severity of the disease [7, 8]. Nonsense, consensus splice site, and frameshift mutations result in the absence or near absence of enzyme activity, leading to the classic form. On the other hand, some missense mutations and cryptic splicing have been associated with residual enzyme activity, explaining the late-onset form [4].

In the classic phenotype, the FD course is characterized by acroparesthesia in the hands and feet, abdominal pain, hypohidrosis, angiokeratoma, cornea verticillate, and exercise intolerance [3] early in childhood [9]. Subsequently, FD progresses to multi-organ damage in adulthood with manifestations including progressive chronic kidney disease (CKD), hypertrophic cardiomyopathy, arrhythmias, heart failure, stroke, and transient ischemic attack [2, 10]. On the other hand, in late-onset phenotype, FD manifestations occur in adults, mainly involving cardiac or renal damage.

FD clinical manifestations may be partly avoided or delayed by specific treatments, i.e., ERT and migalastat

[11, 12]. However, despite these interventions, patients can still experience clinically relevant symptoms [11] due to other pathogenic mechanisms, including inflammation, oxidative stress, and endoplasmic reticulum stress with unfolded protein response [13].

Among these, exercise intolerance is a common and misleading symptom in FD patients throughout the disease [14]. The cause is not well understood, but anemia, pulmonary and cardiac dysfunction, muscle damage, neurological involvement, and the impact of the disease on psychological and psychosocial functioning play a central role [3, 15–19] (Fig. 1).

Exercise intolerance and its resulting diffuse pain can be managed through supportive therapy [20], such as analgesics. However, a promising and challenging new approach involves engaging FD patients in physical activity and exercise training [14]. Therefore, our primary aim was to review the pathophysiology and clinical aspects of exercise intolerance in patients with FD and, secondarily, to explore the role of exercise training and physical activity as supportive therapy.

Exercise Intolerance

Exercise intolerance, defined as the reduced ability to perform activities that involve dynamic movement of large skeletal muscles due to symptoms of dyspnea or fatigue [21], may occur even in the early stages of FD [2]. Indeed, fatigue affects approximately 50% of FD people. In a study assessing chronic fatigue with the Visual Analogue Scale for Fatigue (VAS-F), which is rated on a 100 mm horizontal line ranging from 0 (no fatigue) to 100 (very severe fatigue), an average VAS-F of 6.9 was observed [3]. Interestingly, although FD females often present with milder symptoms than FD males, fatigue and exercise intolerance are more common in female patients [22].

However, little is known concerning exercise and lysosomal illnesses like FD. Pompe disease is the most researched illness in this field. Sechi et al. [23] demonstrated that Pompe patients engaging in moderate-intensity physical exercise improved exercise tolerance. Specifically, the increased peak VO₂, expression of aerobic physical activity was consistent with improved general health and vitality parameters after exercise, and even more significantly after exercise plus diet.

There is only a pilot study on exercise in FD [14] aimed at determining the degree of exercise intolerance and the impact of exercise on FD patients. The exercise capacity and strength of 14 patients (mean age 46 years, six females) were assessed before and after a 12-month strength/circuit

Causes of "exercise intolerance" in Fabry patients

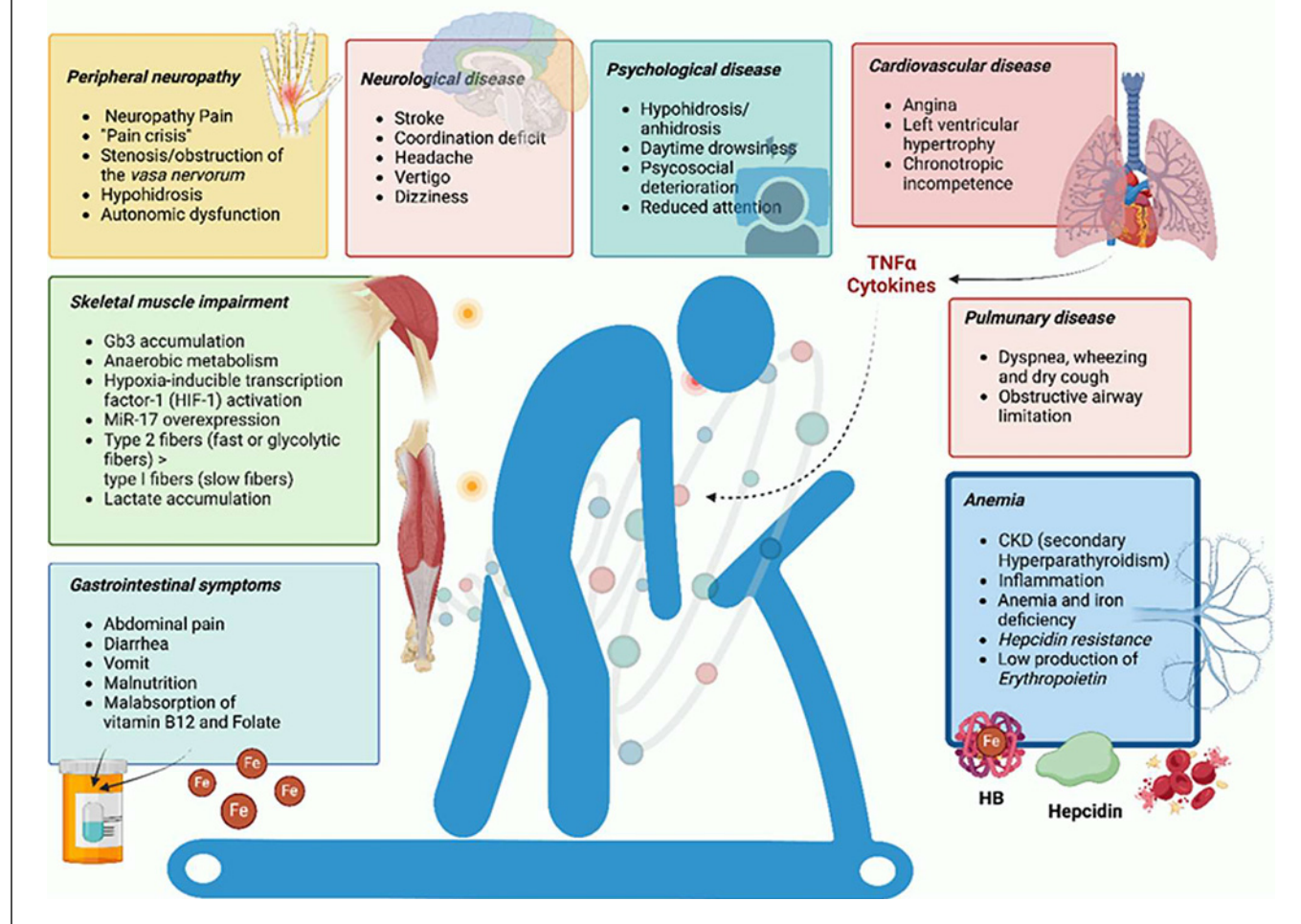


Fig. 1. Pathophysiological mechanisms involved in exercise intolerance in Fabry patients.

exercise training regimen. Participants initially reported typical muscle soreness before starting the exercise program. In contrast, acroparesthesia or pain attacks occurring during exercise were not reported. In 58% of participants, their levels of weariness decreased. Additionally, 67% of FD patients believed the program would be suitable for enhancing their overall fitness and general well-being. This study suggests that individuals with FD frequently avoid physical exercise, impairing their ability to tolerate it. It also indicates the potential benefits of consistent exercise, such as the improvement in overall well-being, muscle strength, and endurance [14].

Moreover, it is noteworthy that exercise intolerance leads to reduced physical activity and physical function,

which young patients perceive as significant limitations for psychosocial development and quality of life [16]. However, these aspects are still poorly characterized and addressed by therapeutic strategies.

Lower exercise capacity in FD patients compared with age-, gender- and size-matched normal controls has been described through cardiopulmonary exercise test (CPET) [15, 17]. Furthermore, a reduced capacity to increase heart rate during exercise, known as chronotropic incompetence, has been observed [17, 22, 24]. Another factor contributing to low exercise tolerance is the lower indexed VO₂ max and peak index oxygen pulse [25].

On the other hand, physical inactivity increases fatigue, frailty and risk of depression while decreasing

Table 1. Pathogenic factors and concomitant conditions contributing the exercise intolerance in Fabry patients

Factor resulting in exercise intolerance					
pathogenic factors	authors, year, country, [reference]	design	sample	mutations	inferences
Skeletal muscle impairment	Pellissier et al., 1981, France [29]	Case report	1 patient, adult male age: 26 yrs	NA	Gb3 inclusions at the sarcolemma and intermyofibrillar levels
	Lu et al., 2023, China [30]	Observational	18 patients, children male: 14 age: 11±2 yrs	n.1: C142R n.2: R112H n.1: N215S n.1: Trp47* n.1: Met1? n. 3: N34H n.1: P259L n.2: R112C n.2: G261V n.1: Trp24* n.1: Trp162* n.1: Glu358del n.1: Tyr152dup	Low skeletal muscle mass
	Gambardella et al., 2023, Italy [31]	Case control	58 patients, adults male: 29 patients age: 42±15 yrs	c.901C>G 40% c.1066C>T 31% c.352C>T 8.3% c.950T>C 5% c.508G>A 5% C.427G>A 3.3% c.680G>A 1.7% c.153G>A 1.7% c.667T>G 1.7% c.388A>G 1.7%	Reduced tolerance to aerobic activity and lactate accumulation
Peripheral neuropathy	Dutsch et al., 2002, New York [32]	Case control	30 patients, adults male: NA age: 29±9 yrs	NA	Painful neuropathy associated with changes in body temperature Reduction in sweating Mild broad-fiber dysfunction (sensory and motor fibers)
	Ramaswami et al., 2006, UK [33]	Observational	82 patients, children/adolescents male: 40 patients age: 12.9 (0.7–17.9) ^a yrs	n.9: Nonsense n.44: Missense n.4: Deletions n.1: Insertions n.7: Others	Exercise as a trigger of neuropathic pain
	Orteu et al., 2007, Europe [34]	Observational	618 patients, adults male: 299 age: 41±14 yrs 134 patients, children male: 30 age: 11±5 yrs	NA	Inability to induce physical activity associated with heat intolerance

Table 1 (continued)

Factor resulting in exercise intolerance					
pathogenic factors	authors, year, country, [reference]	design	sample	mutations	inferences
Cardiovascular disease	Lobo et al., 2008, Australia [17]	Observational	38 patients, adults male: 30 age: 42±11 yrs	NA	Low exercise capacity Inability to reach maximum heart rate during exercise
	Powell et al., 2023, Italy [35]	Observational	44 patients, adults male: 23 age: 38±13 yrs	NA	Increased incidence of arrhythmias at rest and during exercise ST segment and T wave abnormalities on exercise electrocardiography Abnormally low mean maximal heart rate and chronotropic index
	Calcagnino et al., 2011, Italy [36]	Observational	14 patients, adults male: 6 age: 54 yrs	n.1: c.1025delG n.1: R301Q n.1: G208H n.4: N215S n.2: R301G n.1: R301X n.1: A377D n.1: 358del6 n.1: I317T n.1: P343L	Dilated left atrium, increased left ventricular mass, increased relative wall thickness, left ventricular outflow tract obstruction found at exercise echocardiography
	Bierer et al., 2006, USA [24]	RCT	15 patients, adults male: 10 age: 32(20–47) ^a yrs	NA	Reduced exercise capacity
Neurological impairment	Smis et al., 2009, USA - UK [37]	Observational	2,446 patients, adults male: 1,243 age: 43±13 yrs	NA	Functional movement abilities impaired by stroke
	Mendez et al., 1997, USA [38]	Case Report	1 patient, adult male age: 47 yrs	NA	Reduced engagement in physical activity likely due to vascular dementia
Concomitant Conditions					
Anemia and iron deficiency	Kleinert et al., 2005, Austria [27]	Cross-sectional study	345 patients, adults male: 187 age: 40 (23–58) ^b yrs	NA	Reduced physical activity levels for asthenia secondary to anemia
Anxiety and depression	Laney et al., 2010, USA [39]	Observational	33 patientts, adults male: 15 age: 40 (18–59) ^a yrs	NA	Effect of depression on social and occupational functioning

Values are expressed as: mean ± SD; *median (IQR); ^arange; ^bmedian (10th and 90th percentile). NA, not available; yrs, years; Gb3, globotriaosylceramide.

physical function, exercise tolerance, muscle mass and strength, and cardiorespiratory fitness [26]. These factors contribute to a vicious cycle of reduced physical activity, which can be broken by starting an exercise

regimen. Pihlstrøm et al. [3] recently evaluated health-related quality of life in Norwegian FD adults. In the study, higher education was significantly correlated with better physical HRQOL. Education can facilitate

knowledge acquisition and increase motivation to make lifestyle changes, such as engaging in physical activity and/or modifying diet, to reduce symptoms and comorbidities.

Recognizing and addressing factors, such as skeletal and muscular impairment, peripheral neuropathy, and cardiovascular disease, which contribute to the detrimental loop from exercise intolerance to physical inactivity, is essential for improving physical function and well-being in FD patients. In addition to these factors, concomitant conditions, such as anemia, iron deficiency, anxiety, and depression, often observed in FD, even if not directly related to substrate accumulation, may further contribute to that scenario [27, 28] (Table 1) [17, 24, 27, 29–38, 39].

Pathogenetic Factors of Exercise Intolerance

Skeletal Muscle Impairment

Muscle involvement in FD has been studied since the 1980s when muscle biopsies revealed the presence of Gb3 inclusions at the sarcolemma and intermyofibrillar levels [29]. However, in recent years, muscle damage in FD patients has not been extensively studied, and further research is needed [30]. Lu et al. [30] used dual-energy X-ray absorptiometry to assess muscle mass in children aged 6–17 years with classic and late-onset FD [40]. The results revealed a reduction in muscle mass from an early age, likely due to the destruction of muscle fibers by lysosomal deposition and reduced vascularization because of disease-related damage to intramuscular vascular endothelial cells. It has been observed that accumulation of Gb3 in the endothelium or smooth muscle of the vasculature leads to endothelial dysfunction with reduced production of nitric oxide, a strong vasodilator [40]. Gb3 accumulation may also directly involve muscle myocytes [41] and a high glycolytic rate and underutilization of lipids, as fuel, have been recently described in FD skeletal muscle cells [31].

Another study examined the muscle phenotype and altered metabolism in FD mice [31]. Analysis of the study identified a switch to anaerobic metabolism supported by hypoxia-inducible transcription factor-1 (HIF-1) under hypoxic conditions. The activation of HIF-1 under oxygen conditions can be induced by stimuli, such as hormones, growth factors or microRNAs [31]. Specifically, overexpression of miR-17 induces the activation of HIF-1, promoting muscle remodeling with lactate accumulation. The muscle cannot use lipids as fuel, due to altered metabolism in favor of anaerobic glycolysis [31].

This phenomenon has been described not only in mice but also in humans. In 58 FD patients, the exercise duration to reach the maximum peak was assessed using an ergometer cycle and compared with 30 age-matched controls [31]. The study found that FD patients reached the maximal effort earlier than controls, resulting in a shorter exercise duration. Nevertheless, FD patients had a more pronounced increase in lactate levels. Specifically, capillary lactate levels were measured before and after the peak exercise, revealing a more significant increase in peak lactate levels in FD patients than in controls. The authors also explored the histological appearance of muscle from mice with FD [31], revealing a predominance of type 2 fibers (fast or glycolytic fibers), with a scarcity of type I fibers (slow fibers). This finding primarily indicates the presence of anaerobic metabolism in FD patients, impairing their physical performance and increasing fatigue. Second, it suggests an alteration of muscle composition contributing to greater exercise intolerance [31].

Peripheral Neuropathy

Neurological damage may manifest as damage to small fibers of the peripheral nervous system and/or autonomic nervous system (SNA) dysfunction [28]. Small fiber damage results in neuropathic pain, which can be classified as acute or chronic [28]. Acute damage, also known as “pain crisis” or “Fabry’s crisis,” arise as a burning pain in the extremities (hands and feet) triggered by exercise, temperature change, stress, or fever [42, 43]. It is often associated with hypohidrosis, described in 53% and 28% of Fabry males and females, respectively [34], as well as with overheating during exercise. In contrast, chronic neuropathic pain is persistent, involving a continuous burning sensation pain in the extremities [42].

Neuropathic pain, acute or chronic, is a characteristic early symptom in FD patients and is experienced by 60–80% of FD boys and girls [2]. It typically begins at a young age, around 9 years in 60–80% of males and around 16 years in females, occurring in 40–60% of cases [28, 44]. The pathogenesis still needs to be fully understood. GB3 deposits at the level of the dorsal root ganglia likely lead to both stenosis/obstruction of the *vasa nervorum*, resulting in ischemic damage and damage to neuronal cell proteins (e.g., sodium TRPV1 channel proteins) [28, 43, 44]. Early substrate accumulation is crucial in endotheliopathy and small fiber neuropathy, associated with microvascular alterations, hypohidrosis, heat intolerance, and pain episodes triggered by exercise [45].

Autonomic dysfunction is manifested by hypohidrosis and intestinal dysmotility (i.e., cramps, diarrhea, nausea) or reduced heart rate acceleration with the onset of exercise [28, 39]. The neurological involvement of both small peripheral nerves and the autonomic system significantly reduces participation in motor activities in young adults and adolescents [28, 46]. The impairment of the SNA also affects the heart rate, which could influence, in turn, the ability to exercise [35]. However, the role of the heart rate in determining exercise intolerance requires further in-depth research. Specifically, it is necessary to determine the adequate heart rate (HR) level during maximal exercise in FD patients [35].

In a retrospective study by Powell et al. [35], 44 FD patients underwent maximal cardiopulmonary exercise testing. The results were highly heterogeneous depending on which HR value was considered compromised, whether an HR value of <25 bpm/min at 1 min or <12 bpm/min at 1 min after exercise. In the first case (HR <25 bpm/min), 11 out of 44 patients (25%), and in the second case (HR <12 bpm/min), only 2 out of 44 patients showed impairment [35]. Thus, depending on the HR value considered, the impact of reduced HR on exercise intolerance may differ.

Cardiovascular Disease

Cardiac symptoms in FD contribute significantly to exercise intolerance, with multifactorial cardiac-based mechanisms [21]. In an extensive FD registry, including data from 714 patients, the prevalence of angina was 23 versus 22%, palpitations and arrhythmias 27 versus 26%, and exertional dyspnea 23 versus 23% in women and men, respectively [47]. These cardiac symptoms were more frequent in treated patients, reflecting a more severe disease, with a similar frequency in both genders, but with a later onset in women [47]. A higher frequency of cardiac symptoms was detected in the presence of left ventricular hypertrophy [47].

Analyzing these registry data, it is noteworthy that despite angina being very frequent [48], there were relatively few records (5 out of 714 patients) of coronary revascularization procedures or myocardial infarction in this series [47]. These findings should be interpreted cautiously, considering that FD patients with marked left ventricular hypertrophy frequently show pathologic ischemic changes during CPET, indicating possible premature atherosclerotic coronary artery disease, but also microvascular disease or transient oxygen mismatch [35]. In some cases, it has also been demonstrated that left ventricular outflow tract obstruction may be a mechanism of functional limitation during exercise in FD [36].

Another relevant mechanism, as previously described, is the chronotropic incompetence, raising possible concerns about the risks of physical activity in FD patients. However, it has been shown that FD patients undergoing maximal effort CPET had normal recovery of heart rate after exercise, indicating no autonomic dysfunction during recovery [35].

Therefore, considering the established benefits of mild to moderate physical activity in congestive heart failure (CHF) [49] and hypertrophic cardiomyopathy [50], the same principles could be applied to FD patients. Some concerns may arise about vigorous exercise, but it is noteworthy that among 1,160 patients with hypertrophic cardiomyopathy, those engaging in vigorous exercise did not experience a higher rate of death or life-threatening arrhythmias than those engaging in moderate exercise or the sedentary group [51].

Regarding the cardiopulmonary axis, the range of respiratory symptoms, including dyspnea, wheezing and dry cough, is generally attributed to cardiac involvement in FD patients. However, primary lung involvement is also described, with a tendency toward obstructive airway limitation. The mechanisms of this involvement are currently still debated [52, 53].

Neurological Impairment

The central nervous system is one of the main organs involved in patients with FD. According to the FOS database, one of the most comprehensive repositories of FD patient data, cerebrovascular ischemic events, such as stroke or transient ischemic attack, occurs in approximately 12% of male and 27% of female patients [54, 55]. Across different FD cohorts, stroke has been detected in 6.9% and 4.3% of patients. It can impair the functional movement abilities of FD patients by affecting the motor cortex, thereby altering the physical function [2].

Furthermore, cerebrovascular ischemia in Fabry patients could lead to clinically evident cognitive impairment and dementia, alongside psychological and psychiatric symptoms [38, 54, 56]. Neuropsychological impairment and dementia may affect executive functioning, information processing speed, and attention [57]. Meanwhile, psychological, and psychiatric symptoms may manifest as borderline attention, mental slowing, decreased executive functioning, poor memory, and possible depression and suicidal ideation [38]. These neuropsychological deficits can significantly impact the ability to engage in physical activity and exercise. Further studies are needed to define the pathophysiological mechanisms linking cerebrovascular ischemia to neuropsychological impairment in FD patients [54, 58].

It is important to note that although physical inactivity has been identified as a significant yet potentially reversible risk factor for dementia and mild cognitive impairment [59], there is limited data available on the beneficial role of physical activity and exercise in preserving cognitive functions in individuals with normal cognition, mild cognitive impairment, or dementia [59]. Mixed physical activity/exercise was found to be effective in improving global cognition for all types of dementia but not on attention, executive function, memory, motor speed and language [60]. Further research in FD populations should be conducted to explore the potential therapeutic effects of physical activity and exercise on cognitive impairment. Finally, other neurological deficits, such as headache and vertigo/dizziness, can occur in FD patients, ranging from mild to severe, and may limit physical exercise [2].

Others

Gastrointestinal symptoms, like abdominal pain, bloating and diarrhea, may also limit the propensity for outdoor activities. These symptoms have been reported in up to 70% of FD patients, starting early in childhood and presenting with equal severity in females with milder disease [61]. Specific diet interventions showed promising results and may be beneficial for increasing physical exercise in FD patients [62, 63]. More details are described in the therapy section. Similarly, other rarer but severe manifestations of FD, such as ear and ocular disturbances and lymphedema, may impair engagement in outdoor activities.

Concomitant Conditions

Anemia and Iron Deficiency

A characteristic feature of FD patients is asthenia, often secondary to anemia [27]. It is typically normochromic and normocytic, contributing to exercise intolerance. It has been observed in 34% of FD patients, often in association with CKD, CHF, and inflammation [27], with iron deficiency reported in 20% of FD males [64].

It is reasonable to assume that anemia in FD patients is primarily caused by iron deficiency, the most common cause of anemia in chronic inflammatory conditions like CKD and CHF [65, 66]. Iron homeostasis in skeletal and heart muscles is crucial for mitochondrial function and the generation of ATP [67]. Indeed, iron deficiency has detrimental effects on physical performance in patients with CHF [68].

Iron deficiency may be secondary to organ damage in advanced FD, but it may also occur with or without

anemia in the early stage of the disease. Hepcidin resistance and low iron absorption have been suggested as possible mechanisms favoring iron deficiency in FD [64]. Additionally, gastrointestinal symptoms, frequently reported in FD patients, may cause micronutrient malnutrition and low iron intake [27].

A precise assessment of iron status and anemia are still poorly studied in FD patients and not sufficiently highlighted in disease management recommendations [69, 70]. Eventual iron supplementation may be a simple, cost-effective measure to improve the physical function and well-being of FD patients.

Another relevant cause leading to anemia is the presence of CKD [71] (GFR <60 mL/min) in patients on conservative or renal replacement therapy [27]. This anemia is secondary to several processes [72]. First, FD patients with CKD exhibit reduced erythropoietin production resulting in decreased stimulation of erythrocyte production at the bone marrow level [73]. Second, hyperparathyroidism, a common manifestation of CKD, contributes to increased resistance to erythropoietin, mainly if poorly controlled [74]. Third, the chronic inflammation typical of CKD patients leads to increased hepcidin stimulation, resulting in the inefficient use of iron stores [74].

However, Kleinert et al. [27] observed that even 40% of FD patients without CKD (eGFR >60 mL/min) were anemic, and 82% of these patients had heart failure and/or an inflammatory state. Patients with heart failure have an increased cytokine production, interfering with the synthesis of erythropoietin. Specifically, elevated TNF- α activity in decompensated and inflammatory states diminishes renal EPO production and reduces the response to EPO at the bone marrow level [75]. Other factors contributing to reduced hemoglobin levels encompass hemodilution due to decompensation or iatrogenic causes [75]. ACE inhibitors, commonly prescribed as renal and cardioprotective drugs in FD patients with proteinuria and renal and/or cardiac involvement [20, 75], can interfere with erythropoietin production and response [75].

Additionally, FD patients can have gastrointestinal disorders that could interfere with the absorption of vitamin B12 and folate, both essential for red blood cell production [27]. However, there appears to be no difference in anemia between FD patients with and without gastrointestinal symptoms [27].

Anxiety and Depression

Another factor favoring exercise intolerance is the effect of the disease on the psychological and psychosocial aspects [3, 16]. Patients with FD-face have an increased

risk of developing neuropsychiatric symptoms, such as neuropsychological deficits and depression, leading to a significant reduction in health-related quality of life [3].

The exact mechanisms of neuropsychiatric symptoms in FD are not fully understood yet. However, it is believed that sphingolipid deposition in the endothelium of small cerebral vessels causes regional cerebral ischemia. In addition, FD patients manifest bouts of chronic pain and other somatic and psychosocial disorders [76]. Laney et al. [77] showed that FD patients, particularly women, had reduced social-adaptive functioning, problems that were significantly associated with anxiety and depression.

According to a recent review of the literature by Bolsover et al. [57] prevalence estimates of depression in FD range from 15% to 62%, with the most significant study considered to date by Cole et al. [78] ($n = 184$) finding a prevalence rate of 46% (of which 28% were found to have severe clinical depression, and of these, 72% were undiagnosed) [57]. In a sample of FD patients ($n = 16$), 62.5% were found to have some form of psychopathology, including depression [79]. It is present severely in almost 1 out of 3 depressive FD patients [57, 78] and appears to be related to pain, poor relationships, poor health perception, comorbidities, and stroke [80]. Among these, chronic pain is the most common and [78, 81–83] is considered the strongest predictor of depression [17], along with the inability to sweat [78]. However, chronic pain and depression may also be indirectly related by affecting social and occupational functioning, suggesting that depression may be a mediating variable in the coping or adapting mechanism of patients to chronic pain and exercise intolerance [57]. It has been observed that depression could reinforce the association between chronic pain and exercise intolerance [17].

Furthermore, excessive daytime sleepiness [84] and neuropsychological impairment in executive functioning, information processing speed, and attention [57] can also contribute to exercise intolerance in FD patients. While a sedentary lifestyle may be both a risk factor for depression and neuropsychological impairment or its consequence, it is essential to highlight that exercise can exert antidepressant effects by stimulating changes in neuroplasticity, inflammation, oxidative stress, endocrine hormones, self-esteem, social support, and self-efficacy [85].

Recently, Singh et al. observed that any exercise training from 2 to 12 months probably improved depressive symptoms in CKD patients undergoing dialysis (10 studies, 441 participants: SMD -0.65 , 95% CI: -1.07 to -0.22 ; IP = 77%; moderate certainty evidence) and the magnitude of the effect might be more significant, when maintaining the exercise beyond 4 months (6

studies, 311 participants: SMD -0.30 , 95% CI: 0.14 to -0.74 ; IP = 71) [86].

The promotion of physical activity appears very effective for managing symptoms of mild depression and anxiety across numerous populations with chronic disease, including FD patients. Further research may consider exercise as an adjuvant therapy to psychotherapeutic intervention in improving quality of life and depressive symptoms in FD patients.

Specific Therapy

ERTs and Chaperone

The current therapies for FD are enzyme replacement therapy (ERT) and chaperone therapy [87]. Since 2001, two forms of ERT have been approved by the European Agency for the Evaluation of Medicinal Products: agalsidase alpha (Replagal, Takeda) produced in human fibroblasts and agalsidase beta (Fabrazyme, Sanofi Genzyme) produced by hamster ovary cells [87]. ERT formulations are administered intravenously biweekly [87].

ERT acts as the missing enzyme, eliminating Gb3 deposits in various cells and tissues [88]. However, this does not always occur [88]. First, ERT does not cross the blood-brain barrier, which limits its effect on the central nervous system [88]. Second, antibodies can be produced against exogenous enzymes, reducing their activity [88]. Third, the efficacy of ERT depends on the patient's age, clinical manifestations, and the disease phenotype at the time of therapy initiation [88].

In a phase 3 study with agalsidase beta used to treat 58 patients with FD classic form, different therapeutic effects were observed during a 54-month follow-up. Most patients benefited from the ERT with stabilization of renal function. However, in 6 patients, progression of renal function was observed. These patients had common characteristics: age >40 years (4/6), high proteinuria values (>1 g/24 h), and glomerulosclerosis at biopsy [89].

In another retrospective study, the correlation between FD phenotype (classic or late-onset) and clinical events, such as CKD progression, cardiovascular impairment, cerebrovascular damage, or death, was assessed. Results showed that male patients with classic forms had a 5-fold increased risk of clinical events compared with women with late-onset forms [9].

More recently, chaperone therapy has been approved with migalastat, which restores the activity of the endogenous enzyme by correcting the folding of the mutated protein [87, 90]. Migalastat is effective only for certain types of mutations, specifically in amenable patients, about 35–50% of FD patients [11, 90]. “Amenable” means that

Table 2. Characteristics of proposed tests for assessing of physical function in fabry patients

Outcome	Test	Description	Note
Aerobic capacity	Six-minutes walking test (6MWT) [108]	• Patient walks as fast as possible, yet safely, for 6 min along a predeterminate distance • Patient can stop and rest if he/she experiences excessive fatigue or symptoms, but the stopwatch is never stopped • Operator records the distance covered during the 6 min, any symptoms, and any breaks	Pros • Widely used ambulatory test • Demonstrated validity • Accepted prognostic value • Practical and easy • Economic • Safe Cons • Limited applicability to severely frail people for the effort required
	Cycle ergometer stress test [109]	• A resting electrocardiogram (ECG) and blood pressure are recorded • Exercise test starts with continuous ECG monitoring while gradually increasing pedal resistance to escalate exertion levels • Exercise test ends when the patient either reaches the maximum allowed heart rate or exhausts their muscular endurance	Pros • Enables assessment of the heart during intense physical activity Cons • Expensive • Specific equipment and training are required
	Cardiopulmonary exercise test (CPET) [110]	• It involves gradually increasing intensity until exhaustion or the onset of limiting symptoms and/or signs on a cycle ergometer or a treadmill • A joint analysis is made of the expired gases, work and/or effort exerted, and the behavior of hemodynamic variables during the test • Various protocols are available for both healthy subjects and subjects with different pathologies	Pros • Gold standard for cardiorespiratory functional assessment Cons • Expensive • Specific equipment and training are required
Walking speed	Gait speed test [111]	• Patient starts from a standing position and moves 9.0-meter straight path on a level surface at a regular walking pace (walking aids permitted) • Acceleration phase: 2.5-m distances untimed • Time taken to cover the next 4.0 m is recorded using a handheld stopwatch • Deceleration phase: 2.5 m on a standstill • The fastest trial of two consecutive attempts is recorded and expressed in meters per second	Pros • Widely used in clinical practice • Rapid assessment process • Reliable • Economic • Practical for various setting • Suitable for home care environments Cons • None
Lower limb balance and function	Short physical performance battery (SPPB) [112]	• It consists of a battery of three tests 1) Balance assessment in three positions: holding the standing, semi-tandem and tandem positions for 10 s each 2) Gait speed test in 4 m 3) 5-time STS test	Pros • High reliability • Low measurement error • High construct validity • Effective • Practical and easy • Economic • Safe • Indicates in CKD patients Cons • None

Table 2 (continued)

Outcome	Test	Description	Note
	Timed up and go test (TUG) [113]	- The subject is instructed to sit with back against the chair and arms on the armrests - Upon the command "go," he/she stands up, walks at a normal pace to a designed line on the floor, turns around, returns to the chair, and sits down - Timing begins when he/she starts the standing motion and ends when he/she returns a seated position in the chair	Pros - Practical - Objective assessment tool - Minimal equipment, expertise or training are required Cons - Variability of instructions - Validity as an index of mobility in the environment still uncertain
	Tinetti test (balance and gait rating scale) [114]	- It includes several items: (1) balance while sitting and standing, (2) getting up and sitting down from a chair, and (3) length, symmetry, trajectory, and continuity of stride - It is necessary to observe the patient performing these actions to complete the scale	Pros - Gold standard for older patients - Widely used in clinical practice Cons - Inconsistency for different versions with different scoring methods - Issues for validity and reliability
	Sit to stand test (STS) [115]	- The patient must stand up and sit down from a standardized chair without armrests (height 0.49 m), for 5 consecutive times - Upon the signal "ready, set, go!" he/she starts the repetitions as quickly as possible from a seated position with the buttocks in contact with the chair to a full standing position with the arms crossed over the chest - The test ends when he/she completes the fifth STS repetition and returns to a seated position. The time taken to perform the task is recorded using a stopwatch - A variant of the STS is the 30-s STS test	Pros - Simple - Rapid assessment process - Portable - Cost-effective - Space and time-efficient - Safe in older adults Cons - None
Strength	Handgrip [116]	- The patient is seated on a height-adjustable chair with feet supported, shoulders flexed and rotated neutrally, elbow flexed to 90° and forearms in a neutral position - The tested arm rests on a table to support the weight of the dynamometer - The dynamic protocol consists of 12 consecutive maximum isometric contractions of 3 s, with a 5-s rest period between repetitions	Pros - Widely used in clinical practice - Simple - Easy - Time and cost-efficient - Safe in patients with cardiovascular disease Cons - Accuracy varies depending on the appropriate size of dynamometer relative to the hand
	1RM estimated by brzycki formula [117]	- It is applicable to multiple body parts (upper limbs, trunk, and lower limbs) - It is determined using Brzycki's formula, which calculates the one-repetition maximum (1RM) based on the maximum load a patient can lift for 5–8 consecutive repetitions per exercise mode	Pros - Simple - Cost-effective - Easy - Safe in older adults or those with chronic illnesses Cons - Specific equipment is required

Table 2 (continued)

Outcome	Test	Description	Note
	Isokinetic test [118]	- It is applicable to multiple body parts (upper limbs and lower limbs) - It is carried out using a dynamometer that keeps the lever at a constant angular velocity - Various devices and test protocols are available	Pros - Gold standard for strength tests - Mainly used in rehabilitation - Provides a wide range of muscle - Function parameters Cons - Expensive - Specific equipment and training are required
Flexibility	Sit and reach test [119]	- Patient sits on the floor with back and head against the wall, legs stretched out - A helper positions the box against feet (barefoot) - He/she slowly moves as far as possible, holding the stretch for 2 s - The measurement is repeated twice, and the best result is recorded. Slouching is not permitted	Pros - The best option for estimating the extensibility of the posterior thigh muscles - Valid alternative to angle tests for assessing flexibility Cons - Limited validity when estimating lumbar extensibility
	Range of motion test (ROM) [120]	- ROM of a joint is quantified by the number of degrees from the starting position of a segment to final position, including its full range of motion - The most prevalent technique for measuring ROM involves the use of a goniometer	Pros - High accuracy Cons - Limited in presence of soft tissue surrounding the joint - Time-consuming

there is residual enzyme activity ($>0 = 3\%$), and with 20 μg of migalastat, an increase in enzyme activity of at least 20% is observed in the patient's cultured lymphocytes [91]. The advantage is that the administration is oral, every other day and potentially crosses the blood-brain barrier [11, 90].

Several other innovative therapies are under investigation, including second-generation ERT, gene therapy, and mRNA therapy [87]. A pegylated form of agalsidase alpha, known as pegunigalsidase, will be available shortly. Promising preliminary studies [92, 93] suggest not only an efficacy and safety treatment of FD patients like agalsidase beta, but also a reduction in the risk of developing antibodies against ERT, due to the presence of pegylation. This innovative structure could allow for an increased dose to be administered (2 mg/kg vs. 1 mg/kg) to reduce the frequency of administration (1 a month vs. 1 every 14 days) with an improvement in quality of life and compliance of patients, although confirmatory studies are ongoing [94].

Effect of Specific Therapy on Exercise Intolerance

ERT and migalastat seem to have a positive impact on exercise tolerance [91, 95] acting on cardiovascular and neurological FD complications. ERT leads to a long-term

morphological and functional improvement of the heart, with a reduction in septum hypertrophy and an improvement in ventricular function [96]. However, considering that ERT seems to stabilize the myocardial fibrosis without improving left ventricular function, these benefits of exercise tolerance only occur in FD patients who do not have myocardial fibrosis when starting ERT [97]. Bierter et al. [15] evaluated differences in cardiopulmonary exercise test performance among FD patients receiving ERT with agalsidase beta at a dosage of 1 mg/kg/h compared with those on placebo. In the 6 patients on ERT, the authors observed an increase not only in aerobic capacity, expressed as VO_2 peak, but also in stroke volume (SV) and HR. The effects on SV and HR could be attributed to reduced endothelial deposition, allowing for a greater flow or increased SNA activation due to reduced neuronal deposition [15]. However, these conditions reflected a more efficient cardiovascular system [15].

In contrast, no changes/improvements in diastolic blood pressure were observed. Patients with reduced diastolic blood pressure maintained these levels during ERT [15].

Berger's study revealed no significant differences in gas exchange among patients on ERT or placebo, despite FD

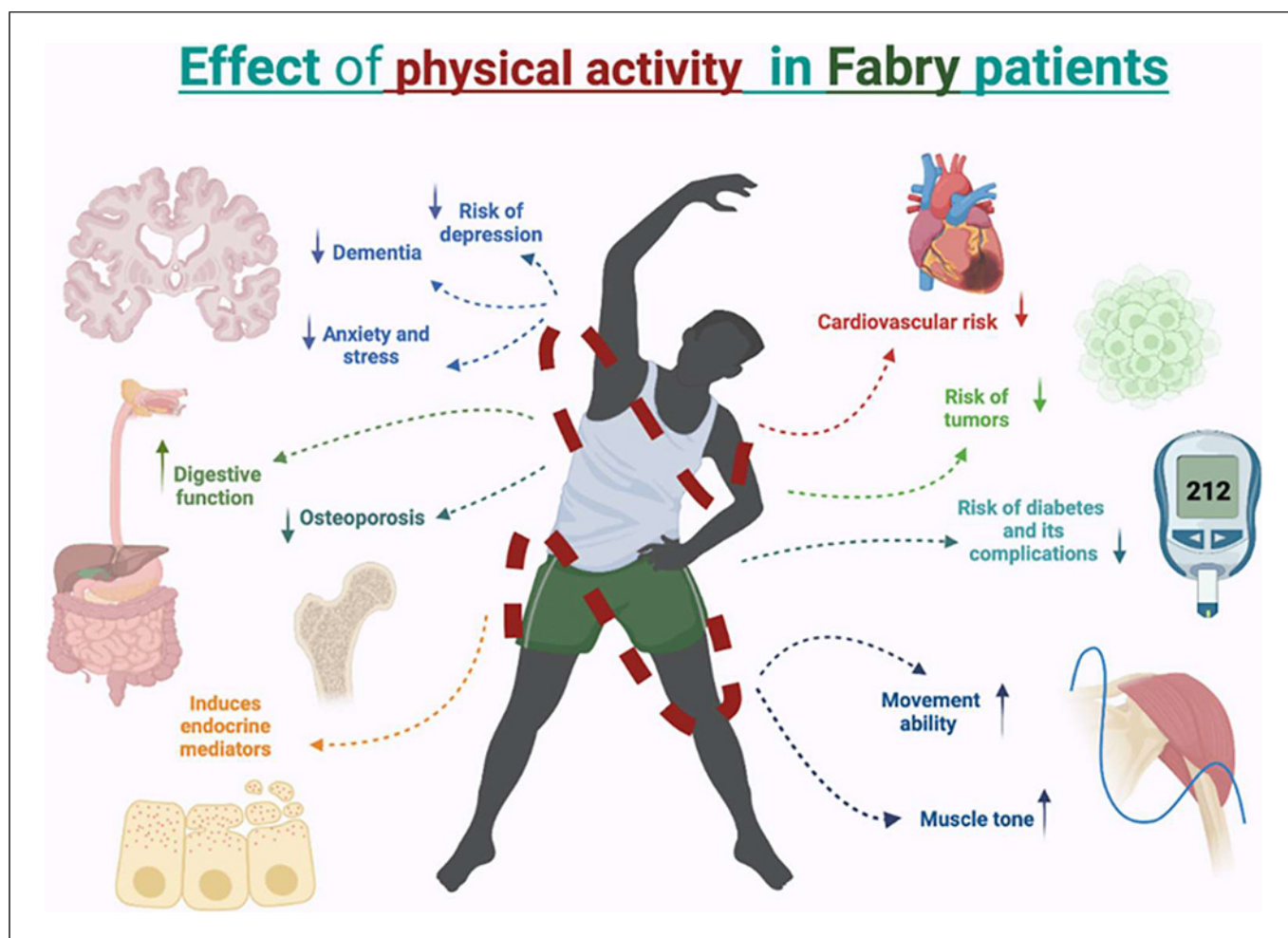


Fig. 2. Benefits of physical activity in Fabry patients.

patients typically having GB3 deposition in the lungs. A possible explanation could be related to the intensity of exercise [15]. In contrast, in a longitudinal study, Odler et al. [98] found positive effects of ERT on obstructive airway disease in 5 patients, with an improvement in forced vital capacity or forced expiratory volume 1. Three patients showed improvement in both parameters.

Regarding chronic and acute neuropathic pain, ERT has been demonstrated to be effective in reducing these, along with other symptoms associated with autonomic system dysfunction, particularly hypohidrosis and gastrointestinal disturbances [99, 100]. It has been observed that the reduction of these SNA symptoms occurred after at least 18 months of treatment with ERT (agalsidase alpha) if the neurological impairment was not advanced at the onset of the treatment [100]. These data confirm that starting ERT earlier leads to multi-organ benefits, including exercise

tolerance [97, 100]. However, there currently needs to be a consensus on when to start ERT, particularly in FD women and/or those with late-onset mutations. However, the general recommendation is to start therapy at the onset of signs and symptoms.

Migalastat also provides significant benefits for exercise intolerance in FD patients [101]. In a study conducted on FD patients, CPET and cardiac magnetic resonance with T1 mapping were used to assess the effect of migalastat on cardiac involvement. After 18 months of therapy, an improvement in cardiac function and an increase in exercise tolerance were found [95].

Role of Exercise as Adjuvant Therapy

Adjuvant therapy was the only option for treating FD patients before 2001, when ERT formulations were introduced. It continues to serve as a supportive treatment

for all FD patients with tissue or organ damage, alongside specific therapy. Drugs, such as renin-angiotensin inhibitors or analgesics, are frequently prescribed to reduce the progression of renal chronic disease and cardiac dysfunction or to alleviate neuropathic pain, respectively. Non-pharmacological approaches, such as specific diets, have also been implemented to control gastrointestinal symptoms. Promising data on the use of a low-Fermentable Oligosaccharides, Disaccharides, Mono-saccharides, and Polyols (FODMAP) diet have been published by Gugelmo et al. [63]. The low-FODMAP involves eliminating fermentable saccharides, which are then gradually reintroduced. In this retrospective study involving 36 FD patients, the low-FODMAP diet significantly reduced GI symptoms, including diarrhea, constipation, and indigestion in FD patients [63].

The evaluation of other FD non-pharmacological approaches, such as physical activity and exercise training, to reduce exercise intolerance and related symptoms, such as fatigue, pain, and dyspnea, has been limited. However, there is growing attention within the scientific community regarding the benefits of physical activity in adults and the elderly with chronic diseases (18 years of age and older). Accordingly, the last World Health Organization (WHO) guidelines, released in 2022, recommend engaging in 150 min of moderate aerobic physical activity per week or 75 min of vigorous aerobic physical activity in sessions of at least 10 min consecutively. Additionally, muscle-strengthening activities involving all major muscle groups should be performed two or more times a week at moderate or greater intensity. For people with reduced mobility, WHO guidelines also recommend activities to improve balance and prevent the risk of falls [102]. Overall, engaging in physical exercise can improve the probability of survival for all causes of death. However, among chronic conditions covered in WHO guidelines, only type 2 diabetes mellitus and hypertension have been included [102]. Nevertheless, it is recommended that FD patients engage in daily aerobic physical activity of submaximal intensity (e.g., walking, swimming, cycling) and endurance to increase cardiovascular fitness and muscular strength [103].

Regarding exercise safety, only one study has analyzed arrhythmic load and heart rate response during exercise programs in FD people. No adverse effects during exercise were reported [35]. Although FD patients can safely participate in exercise training, these data are inconclusive and should be taken with caution, considering the high risk of ischemia alterations and exercise-induced arrhythmias.

Notably, planning an exercise program to improve or maintain an individual's health requires a personalized and accurately established approach. The Frequency Intensity Time Type-Volume Progression (FITT-VP) principle is internationally recognized and aligns with the American College of Sports Medicine (ACSM) exercise prescription guidelines. According to the FITT-VP principle, the composition of an exercise program should be tailored to the individual's needs, limitations, and any modifications of established goals [104].

Moreover, it is advisable to integrate the assessment of cardiorespiratory fitness into routine clinical practice, as emphasized in [105, 106] the ACSM's guidelines [104]. Regardless of age, sex or ethnicity, low cardiorespiratory fitness is a stronger predictor of death than other conventional risk factors [107].

For a comprehensive analysis of physical function in people with FD, an assessment of aerobic capacity, gait speed, strength, lower limb balance, function, and flexibility may be useful (Table 2) [108–120]. Notably, physical inactivity contributes to the development of at least 35 chronic diseases, increasing mortality and reducing health span [121].

Summarizing, incorporating exercise and physical activity into the multidisciplinary management of FD patients characterized by multi-organ involvement [122] is crucial. While recognizing the benefits demonstrated in the general population and other chronic disease settings, further studies are needed to assess the specific impact of exercise and regular physical activity in FD patients. The potential positive effects of exercise include improvements in muscle tone and movement capacity, reduction in osteoporosis and the release of neurohumoral mediators such as serotonin and endorphins, contributing to overall well-being [123].

Engaging in physical activity can also reduce the risk of cardiovascular disease, promote good cardiopulmonary function, lower the risk of certain cancers, and reduce the risk of developing type 2 diabetes by up to 50%. Moreover, it can play a role in preventing hypertension, osteoporosis and osteoarticular diseases. Additional benefits can encompass a decreased risk of cognitive deficits or dementia, alleviation of symptoms related to anxiety, stress, depression, and loneliness, as well as improvements in self-image, self-esteem, enthusiasm, and optimism. Finally, it can also aid in enhancing digestive function, regulating bowel rhythm, and improving muscular strength and endurance, ultimately leading to increased functional capacity for daily activities [123] (Fig. 2).

Conclusion

Exercise intolerance, a common manifestation in FD patients, results from various pathophysiological mechanisms, which include skeletal and muscular impairment, peripheral neuropathy, and cardiovascular disease, significantly impacting the quality of life. Available therapies, such as ERT and chaperone therapy, appear effective in reducing exercise intolerance and its associated systemic symptoms, especially if started earlier in the absence of multi-organ damage. Alongside specific therapy, an increase in the level of physical activity should be pursued following an appropriate evaluation of physical function. It is crucial to plan further multicenter studies to assess the impact of personalized exercise programs on FD patients.

Statement of Ethics

The study has been conducted according to the 1995 Declaration of Helsinki and its revisions. This article does not contain any studies with human or animal subjects performed by any of the authors.

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Concept and drafting of the manuscript: F.B. and Y.B.; writing most of the manuscript: F.B., G.M., and Y.B.; writing part of the manuscript: F.C. and C.M.; final revision: P.E., F.A., N.V., L.P., M.S., A.G., M.T.Z., D.G., M.A., and G.C.; figure editing: M.T.Z.; editing and confirmation of the manuscript: Y.B. All the author have read and approved the final manuscript.

Data Availability Statement

Data statement is not available.

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