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Management of Marfan Syndrome, with a Specific Focus on the Significance of Physical Activity in this Patient Population

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ABSTRACT

Introduction: Marfan syndrome is an autosomal dominant disorder of connective tissue. Timely diagnosis and effective therapy are essential for individuals with Marfan syndrome, as they are susceptible to severe cardiovascular consequences, including aortic aneurysms and aortic dissection. The conventional treatment comprises beta-blockers to mitigate the dilatation of the aorta and aortic surgery. The efficacy of contemporary medicinal and surgical interventions in Marfan syndrome has significantly enhanced mean life expectancy. International guidelines generally discourage physical activity for individuals with Marfan syndrome. Recent recommendations have created exclusions for these patients, indicating benefits from engaging in low-intensity physical activity exclusively.

Aim of the study: The primary aim of this research is to elucidate the most recent management ideas pertaining to Marfan syndrome. Significant emphasis is placed on the importance and safety of physical activity in individuals afflicted with this disease. The risks linked to physical activity are addressed, however the advantages of particular activities are highlighted.

Materials and methods: A review of the literature available in the PubMed database was performed, using the key words: „Marfan syndrome", „connective tissue disease", „physical activity", „aortic aneurysm", „FBN1".

Conclusion: The prognosis for patients with Marfan syndrome has markedly improved in the last years. Contrary to conventional guidance to refrain from physical activity, emerging research indicates that low-intensity exercise may be advantageous. Research on the safety and health implications of physical activity in patients with Marfan syndrome is exceedingly few. Current information indicates that moderate physical activity at a particular intensity may be safe in this condition. Additional study is necessary to offer targeted recommendations for patient training and enhance their long-term quality of life.

Keywords: Marfan's syndrome, connective tissue disease, physical activity, aortic aneurysm, FBN1

1. Introduction

Consistent physical activity is a recognized and successful method for preserving and enhancing health. It is an indisputable component hindering the advancement and management of numerous chronic diseases. Nevertheless, there are illnesses for which physical activity is not typically advised. A subset of heritable connective tissue disorders can be identified among these conditions.

Marfan syndrome (MFS) is an uncommon autosomal dominant genetic disorder. The prevalence of the syndrome is approximated at 1 in 5,000. No differences in prevalence can be found between the sexes or between different ethnic groups [1–3]

The etiology of the Marfan syndrome is a mutation in the fibrillin-1 gene (FBN1)[4]. It is a pleiotropic condition distinguished by particular cardiovascular, ophthalmic, and skeletal characteristics. The predominant cardiovascular complication is aortic root dilation, which, if left untreated, can result in the life-threatening aspect of the disease primarily affecting adult patients.

Without timely diagnosis and treatment, individuals with Marfan syndrome may have an average life expectancy of approximately 40 years. Due to advancements in diagnostics, treatment methods, and medical monitoring, there has been a notable increase in the life expectancy of patients. The variables contributing to the acceleration of aortic dilatation or dissection have been comprehensively elucidated. Factors like as hypertension, intense physical exertion (particularly isometric exercises), and the state of gestation are included [5].

International guidelines generally discourage physical activity for patients with MFS. Recent recommendations have created exceptions for these individuals, indicating advantages of engaging in low-intensity physical activity alone.

2. Clinical manifestation of Marfan syndrome

Marfan syndrome is a systemic connective tissue disorder marked by considerable clinical variability, ranging from modest presentations affecting one or a few systems to severe, rapidly progressing newborn multiorgan illness. It is attributable to pathogenic mutations in the FBN1 gene, which encodes the extracellular matrix protein fibrillin-1 [6]. The extensive range of illness symptoms is associated with the ubiquitous presence of fibrillin-1 in the human body.

The diagnosis of MFS relies on established clinical criteria (Ghent nosology), formulated by international experts to ensure precise identification of this hereditary disorder [7]. Clinical diagnosis may prove difficult as systemic signs can be modest or nonexistent in very young children. Diagnosis may occur in childhood when genetic testing is conducted due to a familial incidence of the condition [8].

The predominant trio of symptoms relates to the skeletal system, cardiovascular system, and ophthalmic system. It infrequently pertains to the respiratory and neurological systems, integumentary system, musculature, and adipose tissues. Nonetheless, the anomalies related to the cardiovascular system pose a danger of reducing lifespan [9] [10] .

Marfan syndrome is a disorder with great penetrance. It is marked by significant diversity in phenotypic expression, as well as fluctuations in symptom intensity among relatives. This variability may be ascribed to the fundamental pathogenic variant [6].

Marfan syndrome can be categorized into two primary forms: early onset Marfan syndrome and the classic Marfan syndrome.

Early-onset (neonatal) is a severe manifestation of the condition [11]. In the majority of cases, the characteristics of Marfan syndrome are observable at birth. The characteristics encompass camptodactyly, arachnodactyly, joint contractures, muscle hypoplasia, and lax skin [12] . Individuals suffering from this illness elevated mortality rates within the initial years of life [6]. Patients experience substantial cardiorespiratory impairment, encompassing congenital emphysema and mitral and/or tricuspid valve regurgitation. It is also known that people with early onset Marfan syndrome typically succumb to congestive heart failure, resulting from significant heart valve regurgitation [11] .

In the classic presentation of Marfan syndrome, the predominant signs arise from the cardiovascular, ocular and skeletal systems [3]. Aortic root dysfunction, resulting in aneurysmal dilation, aortic regurgitation, and dissection, is the principal cause of morbidity and mortality among patients with Marfan syndrome. Dilatation may also affect additional parts of the thoracic aorta, the abdominal aorta, the pulmonary artery root, or even the carotid and cerebral arteries, although this occurrence is far rarer.

Undiagnosed and untreated MFS is often linked to aortic dissection. The dissection typically initiates immediately above the coronary ostia and may extend throughout the full length of the aorta. It is classified as type I in the DeBakey system. A significant number of patients with MFS and aortic dissection possess a familial history of dissection.

Mitral valve prolapse (MVP) is frequently noted in persons with Marfan syndrome [13]. The prevalence of MVP in MFS escalates with age and is more pronounced in women. Tricuspid valve prolapse may also present.

Skeletal signs encompass bone overgrowth and joint laxity, excessively elongated extremities relative to trunk size (dolichostenomelia), rib overgrowth that may result in sternal depression (pectus excavatum) or protrusion (pectus carinatum) and scoliosis that varies from mild to severe. Individuals with MFS exhibit height above that anticipated from their genetic background (without the FBN1 mutation), which is typically, though not invariably, above

average relative to general population standards. In patients with MFS, back pain may be associated with scoliosis or lumbosacral dural ectasia. This occurrence is prevalent, serves as a presenting symptom in approximately 30% of patients, and constitutes a substantial cause of disability .

Symptoms in the eyes include myopia (seen in over half of afflicted individuals), ectopia lentis (present in around 60% of affected persons) and an elevated risk for retinal detachment, glaucoma, and early cataracts [3]. Consequently, annual ophthalmologic evaluations are advised for all patients with MFS. An urgent evaluation is advised for patients experiencing a sudden alteration in eyesight.

Certain people with MFS manifest lung illness. They have emphysematous alterations with lung bullae primarily in the upper lobes, which may predispose individuals to spontaneous pneumothorax.

3. Management of Marfan syndrome

One of the most effective management methods involves the participation of a broad group of specialists working together. Among the specialists that are included in the team of experts can be a clinical geneticist, a cardiologist, an ophthalmologist, an orthopedist, and a cardiothoracic surgeon. Other specialists may also be included as required.

The 2022 American College of Cardiology/American Heart Association guidelines for aortic disease encompass recommendations for Marfan syndrome, Loeys-Dietz syndrome and other genetic syndromes impacting the aorta [14] .

The outlook for individuals with MFS has enhanced due to the implementation of medical treatments (such as beta blockers and angiotensin receptor blockers), regular and noninvasive assessments of aortic dimensions, planned surgical interventions for the aorta, and limitations on intense physical activity. The physiological changes that take place during pregnancy are linked to a heightened risk of aortic dilation and dissection, necessitating more rigorous monitoring.

3.1. Monitoring of the aorta

Aortic root dilation is a distinctive trait of individuals with Marfan syndrome. A constellation of hemodynamic and anatomical factors influences the susceptibility of the aortic root to dilation.

The aorta wall at the sinus level includes a higher concentration of elastin compared to other regions of the arterial system. Consequently, patients with connective tissue disorders characterized by elastogenesis, such as Marfan syndrome, exhibit an elevated risk of aortic dilation at this location. In addition, this section of the aorta is the one that is subjected to the pressure load that is brought on by the ejection of the left ventricle, which also makes it more likely to dilate.

Echocardiography (2D-TTE) is usually used to identify aortic root dilatation. This test is advised for the preliminary diagnosis, clinical assessment, and monitoring of the aortic root and proximal ascending aorta [15]. In accordance with the instructions made by the Marfan Foundation, the Z score is computed using the Roman formula. For the purpose of regression analysis, the aortic Z score, after being adjusted for body height, has been validated and is applied extensively in clinical practice [16] .

More precise measures can be obtained with computer tomography angiography (CTA) and magnetic resonance imaging (MRI). Scans acquired through these technologies enhance comprehension of the aortic structure and, crucially, the peripheral arteries. CTA and MRI offer enhanced precision in instances of lateral wall deformity or asymmetric aortic roots.

Each of these assessments possesses distinct advantages and limits. Computed tomography provides enhanced spatial resolution [6]. Nevertheless, the necessity to reduce exposure to ionizing radiation renders it an unsuitable option in many cases.

Magnetic resonance imaging is favored over computed tomography angiography due to its absence of ionizing radiation and the possibility of being conducted without intravenous contrast. This is especially crucial for ongoing monitoring in youngsters to avert cumulative radiation exposure. CTA is the benchmark for evaluating aortic wall integrity due to its markedly reduced procedure duration. Furthermore metallic implants, even if MRI compatible, can considerably impair image quality. Considering all these factors, non-contrast MRI sequences are advised for the evaluation of the isolated aortic root [6] [14] [17] [18] .

It is advisable to conduct 2D-TTE biannually, unless there is a rapid rise in aortic root diameter in pediatric or adult patients. In such instances, monitoring frequency may be adjusted based on clinical evaluation [19]. When assessing the health state of patients with Marfan syndrome and conducting an echocardiographic evaluation, it is essential to consider the potential for cardiac valve malfunction, particularly on the left side [16].

Annual imaging is advised for individuals with MFS provided that the stability of the aortic diameter is verified. Additional imaging is recommended when the maximal aortic diameter reaches 4.5 cm or exceeds it, or if there is substantial development in aortic diameter

from the baseline measurement. An abdomen CT scan or MRI is advised every 2 to 3 years, while comprehensive imaging of the vascular neck tree and central nervous system is suggested once every 3 to 5 years.

A comprehensive vascular imaging of the thorax and abdomen (from neck to pelvis) is recommended starting at age 18, utilizing CT scan or MRI every 2 to 5 years [15][20].

3.2. Aortic Surgical Intervention

Ascending aortic dilatation is defined as a condition where the diameter surpasses 40 mm. However, per AmericanHeart Association (AHA) guidelines, surgical intervention for the aortic root should be contemplated in asymptomatic patients with Marfan syndrome when the maximum aortic diameter ranges from 45 to 50 mm. Surgery is often conducted when the aorta diameter nears 50 mm. Nevertheless, there are instances where it is advised earlier, specifically when the diameter is below 50 mm. Factors encompass a quick increase in aortic diameter (exceeding 5 mm annually), a concerning family history, and the existence of notable aortic valve insufficiency [14].

The dilated aortic root may be replaced independently (aorta-sparing surgery) or concurrently with the aortic valve (aortic valve replacement surgery). The optimal approach, particularly for younger patients, is the David reimplantation technique - valve-sparing aortic root replacement [21]. This method's advantage is the elimination of the necessity for lifelong anticoagulant therapy, which is especially beneficial for women contemplating pregnancy. Nonetheless, we are concerned about the potential onset of valve malfunction and the necessity for an additional procedure. Mechanical aortic valve replacement is a more enduring alternative. Nonetheless, it poses a risk of thrombosis as well as a danger of iatrogenic hemorrhage [22] .

In 2013, the "PEARS" (Personalized External Aortic Root Support) procedure, a contemporary option for Marfan patients, was introduced, utilizing an external device to stabilize the ascending aorta, permitting it to remain intact. This device is constructed from medical-grade polymer fabric as a three-dimensional replica of the patient's aorta, hence the designation "personalized surgery." During the surgical procedure, it encircles the patient's aorta, and its positioning typically obviates the need for coronary artery bypass grafting while maintaining the blood-endothelial interface. PEARS is contraindicated in patients with greater than mild aortic valve regurgitation. This procedure is typically conducted in individuals with a smaller aortic diameter compared to those receiving valve-sparing surgery.

Aortic root surgery is presently the sole efficacious technique to avert dissection. Thus, when conducted prophylactically, it is the gold standard for individuals with Marfan syndrome exhibiting aortic dilatation [23] . Pharmacological management only decelerates the evolution of aortic dilatation and postpones the necessity for surgical intervention, which is particularly significant in pediatric patients, since premature surgery can result in additional procedures due to the patient's growth and illness advancement.

Prophylactic surgery has a low mortality rate (around 1% in proficient centers), unlike surgeries conducted in emergency scenarios following an aortic dissection [24].

3.3. Pharmacological Treatment

If left untreated, individuals with Marfan Syndrome may exhibit earlier progressive dilation of the aortic root. The enhancement in survival rates can be linked to advancements in familial screening, consistent surveillance, preventive medical treatment, and prompt surgical interventions. It is evident that the composition and biomechanical properties of the arterial wall are modified, leading to heightened fragility. However, reliable biomarkers for predicting aortic events remain elusive. The most reliable indicator continues to be aortic root dilation, which has led to treatment strategies focused on decelerating the growth of the aortic root.

High blood pressure requires proactive management.

Over the years, various classes of antihypertensive medicines have been studied for their effectiveness in slowing aortic dilation in patients with Marfan syndrome: (1) beta-blockers (BB), (2) Angiotensin receptor blockers (ARBs) with and without baseline beta-blockers treatment, (3) ACE inhibitors. The selection of a drug is clearly influenced by a range of factors, including the patient's age and family history of aortic dissection. The preferences of the patient and their tolerance to the medication hold significant importance. Patients diagnosed with Marfan syndrome and confirmed aortic dilatation should receive appropriate doses of BBs or ARBs. In more severe instances, a combination of medications from both categories may be required for effective management.

The initial pharmacological agents employed to avert aortic events in individuals diagnosed with Marfan syndrome were beta blockers (beta adrenergic receptor antagonists). Their impact on alleviating the strain on the aortic wall is applied in this context. These medications continue to be widely utilized to decrease the progression of diameter of aorta enlargement. A 1994 randomized experiment indicated that prophylactic administration of propranolol significantly decreased the risk of aortic dilatation and the occurrence of aortic

problems. Since that time, beta blockers have been regarded as the standard treatment for individuals with Marfan syndrome. The drugs currently utilized in this category include propranolol, atenolol, and metoprolol. Atenolol has emerged as the preferred medication, primarily due to its cardioselective characteristics, along with its extended half-life in comparison to propranolol, and a comparatively lower incidence of side effects. The findings indicated that the drug dosage must be tailored to align with the patient's target heart rate. It is advised to keep the heart rate within the range of 60-70 beats per minute while at rest, and below 100 beats per minute during submaximal exercise [25].

It is important to highlight that the impact of beta blockers on clinical outcomes like aortic dissection or mortality lacks robust evidence. The results of several studies conducted to evaluate the effectiveness of beta blocker treatment in patients with Marfan syndrome have been conflicting [26].

A meta-analysis conducted in 2017 revealed insufficient evidence supporting the long-term use of beta blockers in individuals with Marfan syndrome [25].

Recently, there has been a growing interest in pharmaceuticals that may alter the natural progression of the disease by targeting the signaling pathways associated with the affected aorta. Reports indicate that ARBs, especially losartan, have shown beneficial effects in patients with Marfan syndrome [27] [28] [29]. Investigations involving this drug indicate that heightened the transforming growth factor beta (TGFβ) signaling could be instrumental in several phenotypic characteristics of the syndrome, such as progressive aortic dilatation and lung defects accompanied by bullae. Losartan is a medication that diminishes the activity of TGFβ, which likely results in a decrease in ECM degeneration within the vessel wall. Investigations utilizing mouse models have demonstrated the notable effectiveness of losartan. However, this impact is less evident in human subjects [30].

A meta-analysis conducted in 2022 by Pitcher et al. demonstrated a beneficial impact of ARBs therapy on lowering aortic root z-scores, akin to the outcomes observed in patients administered BBs [31].

It can be concluded that both ARB and BB are effective in decelerating aortic root enlargement. Furthermore, it appears that utilizing combination therapy could yield greater efficacy compared to administering a single medication. The most recent ACC/AHA guidelines indicate that individuals with Marfan syndrome ought to receive treatment with BBs or ARBs, or a combination of both medications at the highest doses that can be tolerated [14]. According to European guidelines, BBs serve as the primary treatment, while ARBs are classified as second-line medications.

Since 2007, the use of Angiotensin converting enzyme inhibitors (ACEI) has been shown to decrease aortic root dilatation in individuals diagnosed with Marfan syndrome [27]. Nevertheless, in comparison to beta-blockers, they do not markedly reduce aortic growth velocity [32]. However, their effectiveness in enhancing aortic distensibility and stiffness, along with a correlated slower rate of aortic growth, has been established. In a manner akin to ARBs, this category of medications has the potential to inhibit or postpone the phenotypic manifestation of MFS by counteracting TGF-β and mitigating or even reducing the fragmentation of the aortic elastic fibers [33]. Currently, the ACEs being utilized are perindopril and verapamil. These may be taken into account for patients who have contraindications to beta-blockers and angiotensin receptor blockers. Concerning the side effects of ACEs, their use is not recommended during pregnancy due to the potential toxicity to the fetus.

Calcium channel blockers are linked to a rise in acute aortic events and should consequently be avoided in patients with Marfan syndrome.

The optimal timing for commencing pharmacological treatment continues to be a subject of significant debate. Some inquiries suggest improved outcomes with early or extended treatment, particularly in pediatric patients with pre-existing aortic root dilatation [27]. Given that aortic root dilatation in Marfan syndrome exhibits incomplete penetration, administering treatment to all patients would result in the unnecessary lifelong management of approximately 20%.

In the management of patients with Marfan syndrome, it is essential to take into account particular relative contraindications to treatment: for beta-blockers, conditions such as asthma, hyperinsulinism, or difficult glucose levels, and for angiotensin receptor blockers, it is important to note women without contraception or infants under the age of 1 year. Comprehensive surveillance of possible adverse effects is required.

4. Physical activity and sports in patients with Marfan syndrome

An individual with Marfan syndrome is typically tall and agile, perhaps engaging in various physical activities and sports, so exposing themselves to the danger of aortic dissection and untimely death. Consequently, it is imperative that the diagnosis is established promptly. Contact and competitive sports present a specific risk. Guidelines for activity restrictions due to cardiovascular issues can be generally applied to all individuals with Marfan syndrome. Furthermore, physical exercises for each individual must be tailored according to their specific ophthalmologic and orthopedic conditions.

Physical activity can generally be categorized into two exercise groups: dynamic exercises (also known as isokinetic) and static exercises (i.e., isometric). The fundamental principle of isokinetic exercises involves alterations in muscle length and joint movement, accompanied by little intramuscular force generation. The isometric exercise type is defined by minimal muscle length alteration while producing significant intramuscular force. Most sports use components of both static and dynamic training. Examples of sports that primarily incorporate isokinetic activities include walking, tennis, and volleyball. Isometric exercises are predominantly observed in weightlifting, gymnastics, and water skiing.

Dynamic activities engage the sympathetic nervous system, subsequently elevating heart rate, stroke volume, cardiac output, and diminishing peripheral resistance. Furthermore, an elevation in systolic pressure and an augmentation in end-diastolic volume can be noted. The impact on systemic blood pressure is mild.

Isometric exercises elevate peripheral resistance, blood pressure, and heart rate, adversely affecting aortic wall tension and increasing the risk of aortic dissection; thus, such exercises are particularly contraindicated for patients with Marfan syndrome.

Physical activity for patients with MFS is generally not suggested or is severely restricted in intensity (e.g., golf, bowling, walking). American standards advise that individuals with Marfan syndrome engage exclusively in low-intensity physical activity [34]. The authors of these suggestions highlight the elevated risk of acute aortic events linked to elevated blood pressure during physical exertion. Furthermore, it is important to highlight that the ascending aorta and the aortic isthmus are frequently impacted by the condition, which correlates with a predisposition to elevated vascular pressure.

Individuals with Marfan syndrome who also possess a bicuspid aortic valve exhibit an increased aortic root diameter, which contributes to the advice against physical activity in this condition [35]. Competitive sports are completely discouraged for Marfan patients. When addressing appropriate activities for individuals with Marfan syndrome, it is essential to remember the mental stress that may accompany competitive athletics. Emotional stress correlates with sympathetic activation and catecholamine secretion.

The National Marfan Foundation (1-800-8-MARFAN) disseminates a leaflet titled Physical Education and Activity Guidelines, which outlines safe exercise regimens for individuals with Marfan syndrome. The most significant among them can be encapsulated. People with Marfan syndrome should:

- prefer noncompetitive, isokinetic exercises conducted at a low-intensity aerobic speed;

- reduce abrupt halts, swift directional shifts, or collisions with other players, apparatus, or the surface;
- maintain an aerobic workload at around 50% of capacity; if the individual is administered a beta-blocker, aim to maintain the pulse rate below 100 beats per minute; Maintain the pulse below 110 if not administered a beta-blocker;
- refrain from engaging in isometric activities, including weightlifting, ascending steep inclines, gymnastics, and performing pull-ups; numerous repetitions at minimal resistance are superior to a limited number of repetitions with greater weight;
- avoid testing their boundaries;
- refrain from engaging in activities that may induce abrupt fluctuations in atmospheric pressure (such as scuba diving or flying in unpressurized aircraft).

It is noteworthy that, over the past three decades, the issue of the suitable level of physical activity for individuals with Marfan syndrome has consistently resurfaced in talks among experts treating these patients [36]. The prognosis for patients with Marfan syndrome has markedly improved. With early diagnosis of the disease, adherence to current treatment guidelines, meticulous execution of preventive tests, ongoing specialized oversight and prompt surgical intervention where required, patients with Marfan syndrome can anticipate a life expectancy exceeding 70 years.

Exercise and physical exercise are crucial for sustaining fitness in the overall population, not alone in individuals with Marfan syndrome. It is widely recognized that they positively influence blood pressure, bone density, and the maintenance of an optimal body weight. Consequently, the significance of safe and suitable levels of physical activity in this condition has grown increasingly vital in recent years, as individuals with Marfan syndrome frequently reach advanced age.

So far, it has been said that physical activity should be avoided among patients with Marfan syndrome. Recently, some exceptions have been introduced in the latest recommendations for these patients, suggesting the benefits of performing only low-intensity physical activity. There is a consensus among professionals regarding the essential importance of a multidisciplinary approach to rehabilitation for Marfan syndrome [37].

In 2017, Benninghoven et al. conducted an observational study among patients with Marfan syndrome. They implemented a three-week inpatient rehabilitation program for MFS patients at the Muehlenberg-Clinic. They evaluated the medical safety and the program's effects on participants' physical fitness and psychological wellbeing through an observational pilot

study. The extensive multidisciplinary program encompassed medical, physiotherapeutic, psychological, and social aspects. This study introduced novel approaches in managing MFS patients through physical activity and sought to examine the impact of training intensity on MFS. The rehabilitation plan for each study participant was, naturally, preceded by a comprehensive individual physical assessment. The authors put forth a training protocol consisting of the following components: daily 30-minute ergometer training, 60 minutes of gymnastics four times a week, 60 minutes of weight training three times a week and 30 minutes of Nordic walking three times a week. The overall length of the training program was 3 weeks, consisting of 5 training sessions. Furthermore, the authors suggested incorporating a personal psychotherapeutic aspect. Maximal blood pressure and target training heart rate were assessed during exercise. The criterion for halting the effort was established at a systolic blood pressure of 160 mmHg. A protocol involving light intensity physical activity appears to yield positive effects. Significant effects on the parameters of the maximum power developed on an ergometer have been recorded, indicating a rise of 42% according to their evaluation standards. Additionally, there was a 39% increase in walking distance, which was measured at 2356 meters with a standard deviation of 666 meters, which was also reported as having a significant effect ($p<0.001$). This study has established the feasibility and safety of training within the framework of MFS in humans [36].

Research is also being undertaken on the effects of physical activity on animal models of Marfan syndrome. Gibson et al. demonstrated in their study that physical activity, whether through forced treadmill exercise or voluntary wheel use, significantly enhances the anatomical aorta's architecture in a mouse model of MFS. The tensions are alleviated, permitting the cessation and reduction of dilatation [38].

In a separate study, Mas-Stachurska et al. revealed that training inhibited aortic root dilatation and partially reversed cardiac hypertrophy in a mouse model of Marfan Syndrome [39].

Presently, data indicates that physical activity at a moderate specific intensity may be safe for patients with Marfan syndrome. Customized physical exercise may be advantageous for people afflicted with this disease and could be recommended as a viable and secure therapeutic strategy in the future.

5. Summary

Marfan syndrome is an autosomal dominant genetic disorder with a prevalence of 1 in 5,000. It is a systemic connective tissue condition with a wide phenotypic spectrum. The

syndrome is characterized by cardiovascular, ophthalmic, and skeletal characteristics. The primary cardiovascular complication is aortic root dilation, which can lead to life-threatening complications if left untreated. International guidelines generally discourage physical activity for MFS patients, but recent recommendations suggest low-intensity physical activity is beneficial.

Undiagnosed and untreated MFS is often linked to aortic dissection. Mitral valve prolapse is also observed in MFS. Skeleton signs include bone overgrowth and joint laxity, excessively elongated extremities, rib overgrowth, and scoliosis. Symptoms in the eyes include myopia, ectopia lentis, and an elevated risk for retinal detachment, glaucoma, and early cataracts. Certain people with MFS manifest lung illness.

Effective management involves a broad team of experts working together. The outlook for individuals with MFS has improved due to medical treatments, regular assessments of aortic dimensions, planned surgical interventions, and limitations on intense physical activity. Echocardiography (2D-TTE) is used for preliminary diagnosis, clinical assessment, and monitoring of the aortic root and proximal ascending aorta. Computer tomography angiography (CTA) and magnetic resonance imaging (MRI) provide more precise measures.

Surgical intervention for the aortic root should be contemplated in asymptomatic patients with Marfan syndrome when the maximum aortic diameter ranges from 45 to 50 mm. The dilated aortic root may be replaced independently (aorta-sparing surgery) or concurrently with the aortic valve (aortic valve replacement surgery). The "PEARS" (Personalized External Aortic Root Support) procedure was introduced in 2013. Advances in familial screening, consistent surveillance, preventive medical treatment, and prompt surgical interventions can enhance survival rates. The most dependable indicator for predicting aortic events remains aortic root dilation. High blood pressure requires proactive management.

Beta-Blockers (BB) are initially used to prevent aortic events in Marfan syndrome patients. Current medications include propranolol, atenolol, and metoprolol. Atenolol is preferred due to its cardioselective characteristics and lower side effects. Angiotensin Receptor Blockers (ARBs), especially losartan, have shown beneficial effects in Marfan syndrome patients. Losartan decreases the activity of TGFβ, reducing ECM degeneration within the vessel wall. A meta-analysis in 2022 showed a beneficial impact of ARBs therapy on lowering aortic root z-scores. Since 2007, Angiotensin converting enzyme inhibitors (ACEI) have been demonstrated to reduce aortic root dilation in patients diagnosed with Marfan syndrome. However, relative to beta-blockers, they do not significantly diminish aortic growth velocity.

Calcium channel blockers are associated with an increased incidence of acute aortic events and should therefore be avoided in individuals with Marfan syndrome.

American standards advise low-intensity physical activity for Marfan patients due to the risk of acute aortic events and elevated blood pressure. The National Marfan Foundation provides safe exercise regimens for Marfan patients, including noncompetitive, isokinetic exercises, reducing abrupt halts, maintaining an aerobic workload, avoiding isometric activities, and avoiding activities that may induce abrupt atmospheric pressure fluctuations.

The prognosis for Marfan syndrome patients has improved significantly over the past three decades. Exercise and physical activity are crucial for maintaining fitness, especially in individuals with Marfan syndrome. Despite traditional advice to avoid physical activity, recent studies suggest low-intensity physical activity can be beneficial. A multidisciplinary approach to rehabilitation is essential for Marfan syndrome patients. An observational study conducted in 2017 evaluated the medical safety and effects of a 3-week inpatient rehabilitation program for Marfan syndrome patients. The study found that light intensity physical activity led to a significant increase in maximum power and walking distance. Research on the effects of physical activity on animal models of Marfan syndrome supports the feasibility and safety of training within the framework of Marfan syndrome in humans. Current data suggests that moderate specific intensity physical activity may be safe for patients with Marfan syndrome.

Disclosure

Author’scontribution: Patrycja Jędrzejewska-Rzezak
Conceptualisation: Patrycja Jędrzejewska-Rzezak
Methodology: Patrycja Jędrzejewska-Rzezak
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