9. the real benefits

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The Real Benefits Of Exercise in Marfan Syndrome Associated Aortic Dissection Base on FITT Exercise Prescription Method

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Abstract:
Marfan Syndrome (MS) is an inherited autosomal dominant disease involving connective tissue. While aortic dissection remains the first cause of death in patients with MS, it remains controversial whether patients can perform physical activities or are not associated with aortic dissection. Several studies/guidelines have shown that exercise has beneficial effects on the aorta. This review discusses and provides exercise prescriptions for MS patients by prioritising their safety. We designed an exercise prescription in FITT method (frequency, intensity, time, and type) based on several guidelines and some results of studies related exercise to MS. This prescription aims to encourage patients with MS to improve their physical and mental condition.

PALABRAS CLAVE

Síndrome de Marfan
Disección aórtica.
Rehabilitación.
Prescripción de ejercicios.

Los verdaderos beneficios del ejercicio en el síndrome de Marfan Base de la disección aórtica asociada al método de prescripción de ejercicio FITT

Resumen:
El síndrome de Marfan (SM) es una enfermedad hereditaria autosómica dominante que afecta al tejido conectivo. Aunque la disección aórtica sigue siendo la primera causa de muerte en los pacientes con SM, sigue siendo controvertido que los pacientes puedan realizar actividades físicas o que no se asocien a la disección aórtica. Varios estudios/directrices han demostrado que el ejercicio tiene efectos beneficiosos en la aorta. Esta revisión discute y proporciona prescripciones de ejercicios para los pacientes con EM priorizando su seguridad. Se diseñó una prescripción de ejercicios en el método FITT (frecuencia, intensidad, tiempo y tipo) basada en varias directrices y algu-

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nos resultados de estudios relacionados con el ejercicio para la SM. El objetivo de esta prescripción es animar a los pacientes con SM a mejorar su condición física y mental.

Introduction

Professor Antonie Marfan, a French paediatrician, firstly described Marfan Syndrome in 1896[1]. Marfan Syndrome (MS) is an autosomal dominant inherited disorder, with 75% inherited diseases and 25% new mutation cases. It is caused by the FBN1 mutation gene. This gene encodes fibrillin-1, a member of the fibrillin family in human protein. It is known that fibrillin is the primary structure of microfibrils and plays its role to provide elastin deposition in the human body[2].

This protein has an essential role in forming the extracellular matrix (ECM). It involves regulating the bioavailability of growth factor β (TGF-β) receptor-1 on chromosome 9 and receptor-2 on chromosome 3[3]. Mutation of FBN1 causes overactivity and overexpression of TGF- β resulting in an imbalance of ECM and vascular remodelling. This abnormal signalling process increased the activity and expression of matrix metalloproteinase (MMP) 2 and 9. Collagen and elastin of the matrix are degraded by MMP and cause an aortic aneurysm and lead to aortic dissection[4,5]. This mutation affected many connective tissues, including the respiratory, ocular, musculoskeletal, and cardiovascular systems[2].

This syndrome occurs in 2-3 out of 10000 individuals[6]. National data from Pusat Jantung Nasional Harapan Kita in Jakarta, Indonesia, reported 39 cases in 2006-2012, and 6 cases including aortic valve surgery[7]. The survival rate of these patients is still low compared to the general population. A study in Norway described that men had about 8x higher risk of death than women (about 4x higher). This study also concluded that men had a median survival rate of 63 years compared to women at 73 years[8].

Marfan Syndrome has three main characteristics; aneurysm of thoracic aortic (TAA)/dissection (TAAD), ectopia lentis, and other systemic manifestations with two genetic characteristics. The first-degree family had been diagnosed by Ghent-2 criteria and FBN1 mutation. The diagnosis can be made using Ghent-2 criteria (Table I) that are easier than previous criteria (Table II)[2,9].

MS has many clinical manifestations associated with fibrillin. The skeletal system may feature tall, disproportionately long arms, legs, fingers, arachnodactyly, an abnormally curved spine, and pectus abnormalities[10]. The ocular system may manifest with ectopia lentis, in the pulmonary system may affect pneumothorax, other organ system affected is skin striae, very loose skin.

Cardiac manifestations include aortic dilatation that may lead to aortic dissection, mitral regurgitation (MR), tricuspid regurgitation (TR), dilatation of pulmonary artery (PA), and cardiomyopathy[1,11]. Children with valvular abnormalities may increased higher risk of endocarditis.

Patients with MS have complications in the mitral valve. The prevalence of mitral valve prolapse (MVP) is 40%, and severe MR is 12%[12]. MR causes volume overload in the left atrium and ventricle related to congestive heart failure[11]. Dilatation of PA was also reported significantly in patients with MS, leading to PA aneurysms in 15,3% of Marfan's patients[13,14]. MS is often associated with the bicuspid aortic valve (BAV). BAV is often related to Thoracic Aortic Disease (TAD), including aortic aneurysms and dissection. People with BAV usually have a larger diameter of the aortic root and ascending aorta[15].

The aortic root occurs only with slight enlargement in normal athletes, so the incidence of sudden death in athletes is infrequent. Arrhythmias are life-threatening manifestations of this syndrome caused by abnormalities of microfibrils in the myocardium, leading to impaired cardiac conduction[11,16]. Ventricular arrhythmias and non-sustained ventricular tachycardia (VT) occurred in 21% of patients. Another study reported that approximately 6.5% cases had sustained VT, and 2.1% of MS patients had sudden cardiac death[17,18].

One of the most important manifestations is the dilatation of the aorta. This aortic dilatation occurs in 60–80% of patients, 50-60% of adults, and 50% in paediatrics. It leads to an aortic aneurysm[2,19]. Another study reported that 50% of patients with MS had dissection of the aorta at <40 years and 2% at > 40 years[20]. There are two important components in the aortic wall formation; elastin fibres and collagen fibrils that cause the aortic wall to become elastic.

However, there is disorganisation of elastin and fibrils in MS patients, weakening the aortic wall[16]. Strenuous activity and heavy exercise will increase the aortic diameter related to increased heart rate (HR) and blood pressure (BP)[21]. During dynamic exercise, peripheral vascular resistance and diastolic pressure will be decreased. Based on that, patients should avoid high-intensity static exercise and contact sports, leading to a high risk of aortic dissection[22].

Rehabilitation in Marfan Syndrome

Rehabilitation is an activity or process to help patients with serious illnesses or disabilities who require medical treatment to give their fullest potential for their physical, psychological and social abilities rather than focusing on their diagnosis[23].

Rehabilitation can be given in various situations, whether outpatient or inpatient, in the hospital or clinic, individual or communal setting. People with MS need to be rehabilitated to improve physical and mental health.

Table I: Ghent 2 criteria for Marfan Syndrome diagnosis[2].

No family history	With family history
AD (Z ≥2) + EL	EL + family history
AD (Z ≥2) + FBN1 mutation	Systemic score ≥7 points + family history
AD (Z ≥2) + systemic criteria score ≥7 points	AD (Z ≥2 for >20 y.o, ≥3 for <20 y.o) + family history
Mutation of FBN1 + EL with AD	

Note: AD= aortic dilatation; EL= ectopia lentis; y.o = years old. No family history: 4 criterias. With family history: 3 criterias.

Table II: Systemic criteria score[9].

Sign	Score
Wrist and thumb sign	3 (wrist OR thumb sign =1)
Pectus carinatum	2
Pectus excavatum/ chest asymmetry	1
Hindfoot deformity	2
Plain pes planus	1
Pneumothorax	2
Dural ectasia	2
Protrusion of acetabuli	2
Reduce US/ LS, increase arm/height, and no severe scoliosis	1
Scoliosis / thoracolumbar kyphosis	1
Reduced elbow extension	1
Facial features 3/5 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)	1
Skin striae	1
Myopia > 3D	1
Mitral valve prolapse	1
Max total 20 points; if score ≥7 indicates involve systemic criteria	

Note: US/ LS = upper segment/lower segment.

Therefore, they should be encouraged to do physical activity. National Marfan Foundation has made physical guidelines for patients with MS. They ensure that the patient can perform the exercises safely and get the maximum benefit without worsening their condition[24].

Rehabilitation in physical exercise has the following advantages: optimising functional capacity regardless of the chronicity of the disease and improving cardiorespiratory work[23,25]. Physical activities are a therapeutic option that has been investigated by experts related to aortic remodelling[26]. However, MS patients need to be alert to do physical activities related to aortic dilatation instead of preventing aortic dissection. The aortic root in MS is stiffer than in normal individuals[16].

Benefits of Exercise in Marfan Syndrome

A case report by Gibson et al. used six Marfan's mice and six control mice. There are three groups; voluntary cage-wheel (they have no limit exercise and can use running wheels during the day/ night), forced treadmill (treated to mild aerobic exercise at 55% capacity), and sedentary (no exercise) lifestyle. The forced group was exercised at

55%, 65%, 75%, and 85% VO2max in 5 times/week for 30 minutes or until exhaustion for five months. This research showed that the voluntary and forced groups had shaped normal sigmoidal with a rising fibre length and reduced aortic elastin fragments. Both groups showed a thickening of elastic fibres in the aortic wall compared to the sedentary group[4].

The effect of exercise related to pressure and diameter in the aortic wall showed that routine exercise can prevent aortic wall weakening and reduce aortic diameter compared with the control group, preventing aortic dilatation. Both voluntary and forced groups showed a significant improvement in the elasticity of the aortic wall.

The data also showed a significant reduction in elastin fragments and disorganisation in the aortic wall with exercise intensity between 55-65% but the group with 75-85% intensity is not as beneficial and effective as the mild intensity (55-66%). However, no effect on TGF-β and Phos-Smad2 expression in the mild (55%) or high (85%) intensity exercise. TGF-β and Phos-Smad2 are indicators to measure the level of MMP 2 and 9. These enzymes are increased in MS aortic than in control. Overall, exercise at a low intensity of 55% of VO2 max had a protective effect on Marfan's aortic mice[4].

A protective effect on regular exercise causes a decrease in elastic fragments and expression of MMP 2 and 9 in the aorta, leading to blockage of elastin fragments and aneurysm progression[4].

Another case-control study by Stachurska et al. reported moderate dynamic exercise to mice gave a good outcome, including a reduction in aortic diameter, LV dilatation, and hypertrophy[27]. Regular low-moderate exercise also has a good effect on aortic prevention leading to aortic dissection associated with sudden death in MS patients besides physical capacity and strength improvement[23].

Harm Effect of Exercise in Marfan Syndrome

Despite the benefits, exercise in Marfan's patient can lead to bad things if done without considering several related conditions. According to Vanem et al., cardiac manifestations is the main cause of death for Marfan's patient. 11 out of 18 patient died due to cardiovascular problem, 6 of them were due to aortic dissection as the leading cause of sudden death[27].

Marfan's athletes involved in high-intensity exercise are particularly vulnerable to sudden death due to aortic dissection. One case of US Olympic volleyball star, Flo Hyman, died in 1986 at 31 age from a fatal aortic dissection. She had suffered from undiagnosed MS. Another story from a teammate of Maryland's basketball, Chris Patton, who died because of aortic rupture at age 21 with typical signs of MS.

MS is often associated with BAV, which usually has a larger diameter of the aortic root and ascending aorta[28]. If the patient does high impact/contact sport/isometric exercise, it will increase the risk of aortic dissection. When doing isometric exercise, during the strain phase, there will be a decrease in venous return from an increase in intrathoracic pressure cause decreasing cardiac output, compensated by increasing HR and vasoconstriction blood vessel.

However, the strain-free phase will dramatically increase venous return, causing a BP spike due to increased cardiac output. Based on that, patients should avoid exercise that can cause BP spikes because it increases aortic wall pressure, leading to aortic rupture. Aortic enlargement can occur due to repetitive hemodynamic overload response associated with exercise.

This makes sense that MS patients should avoid contact strenuous, isometric exercise. A study reported by Cheng Owen et al. showed that weightlifting or intense, strenuous exercise is related to aortic dissection. Based on that study, isometric exercise has a higher aortic dissection risk among those with inherited aortopathies syndromes[29].

Type of Exercises

There are four types of exercise[24,25,30]:

- Aerobic/ cardio exercise

This is a low-intensity exercise that can be done over a long period. This exercise stimulates and strengthens the heart and lungs and optimises the utilisation of O2 in the body. Such as swimming, walking, and cycling.

- Anaerobic

This is high intensity and shorter in duration, only in 2 minutes, and involves muscle strength, including weight training or sprinting. Anaerobic requires higher O2 post-exercise than aerobic.

- Dynamic (isokinetic)

Exercise by moving all muscle components or rhythmic muscular, such as throwing the bowling ball.

- Statis (isometric)

Exercise without moving while the muscle is contracted. Such as weightlifting, will an increase BP than dynamic exercise

Recommendation Exercises in Marfan Syndrome

ESC 2021 recommended that all patients with congenital heart disease perform physical exercise regularly with moderate intensity[31]. To ensure patient safety, it is necessary to monitor HR, BP, and electrocardiogram (ECG).

Exercise prescriptions are highly recommended to ensure Marfan's patient exercises safely based on the data above. This prescription should be individualised to the patient's condition following these parameters; ventricular function measured by echocardiography/ CMR, pulmonary artery pressure, aortic dimensions (contact sports are not allowed by those in aortic diameter >5cm), arrhythmias, and O2 saturation[27,31].

Another study recommends to performed low-moderate dynamic exercise and maintaining HR <110 beats

per minute (bpm), HR <100 bpm when taking beta-blockers and 160 mmHg of the target systolic BP[25,32].

Patients with MS should be encouraged to maintain an aerobic phase at about 50% of capacity[24]. A case-control study by Gibson et al. performed that high intensity 85% VO2max had no protective effect on the aorta in Marfan's mice. Lap swimming is also not recommended for MS patients because it is classified as a high dynamic intensity exercise that requires >70% of capacity (Table III).

Table III: The following table of the recreational/non-competitive sport/exercise recommended by the AHA (2004) for Marfan Syndrome[33].

Permitted	Intermediate	Strongly discouraged
Modest hiking (MI)	Basketball (HI)	Bodybuilding (HI)
Tennis double (MI)	Running (sprinting) (HI)	Hockey (HI)
Treadmill/stationary bicycle (MI)	Skiing (downhill) (HI)	Rock climbing (HI)
Bowling (LI)	Soccer (HI)	Windsurfing (HI)
Golf (LI)	Tennis (single) (HI)	Surfing (MI)
Snorkelling (LI)	Baseball/ softball (MI)	Weightlifting (MI)
Brisk walking (LI)	Biking (MI)	Weights (non-free weight) (LI)
	Motorcycling (MI)	Scuba (LI)
	Jogging (MI)	
	Sailing (MI)	
	Swimming (lap) (MI)	
	Hiking (MI)	
	Horseback riding (LI)	

Note: LI = low intensity; MI = moderate intensity; HI = high intensity.

The Goal of Exercise in Marfan Syndrome

The primary goal of exercise is to reduce dilation of the aortic root leads to aortic dissection, which remains the primary cause of death. Furthermore, mitigate cardiac hypertrophy and improve signs of cardiac overload[27].

Dynamic exercise can also reduce psychological stress, and somatisation persists through 1-year follow-up[32]. Based on Marfan Foundation, regular exercise improve both physical and emotional well-being[24].

The Prescription

Improvements in medicine, technology, and pharmacology have developed rapidly in the management of MS, and rehabilitation improved patients' quality of life with disabilities/chronic diseases[33,34]. The primary purpose of the exercise is to optimise functional capacity, quality of life improved, and delay the further deterioration of MS. Physical exercise should be an essential part of their management[25].

However, on the other hand, MS has exercise limitations due to manifestation in the musculoskeletal system, especially in the cardiovascular system. Patients with MS have a higher risk dilatation of the aorta and dissection caused by increased BP and HR[29]. Patients with Marfan will ask what exercises are safe, how many times they exercise in a week, what intensity of exercises is safe[24].

Frequency

The National Marfan Foundation publishes a pamphlet of *Physical Activities Guidelines* which describes safe exercises program for MS. They recommend choosing any enjoyable activities 4-5 times a week for 30 minutes[24]. Malek et al. also designed a program for rehabilitation in patients with TAD. They are set 3 times/week and 20-60 minutes per session[21].

Prescription exercise that has been made by Certo et al. performed a good outcome for a 17-year-old male Marfan patient. They are divided into two kinds of exercises: strength and aerobic training by applying aerobic exercise 4-5 times a week for 10-30 minutes per session within in 3 weeks and low load resistance training for 3 days a week. It showed an improvement of physical capacity and increased strength[25].

Although only a few studies/research discuss how often should take exercise in patients with Marfan, we recommend taking exercise regularly 4-5 times a week based on Marfan Foundation. Regular exercise help improve physical and emotional well-being. It helps the

aortic walls become stronger and prevent them from rupturing due to mechanical stress[24].

Intensity

Marfan's patient was encouraged to keep in low to moderate exercise intensity with a range of METs (<6 METs) (Table IV). Patients with MS should be maintained HR <100 bpm. Allow in 50% of aerobic level capacity and properly do the correct breathing technique[24].

Marfan's patients are encouraged to exercise in low-moderate intensity, regularly monitoring echocardiography every 6 months, although there is no evidence of aortic root dilatation[28]. Patients with Marfan should avoid rapid changes in systolic blood pressure (SBP). Rapid surges in SBP will place significant transient strain on the aorta. It seems reasonable for patients with MS as those with an aneurysm ought to avoid the rapid swing of BP[29].

Patients with MS also avoid intense high-intensity exercises due to aortic enlargement as a response to hemodynamic overload. Meanwhile, a study published by Mas-Stachurska et al. reported that mild-moderate dynamic exercise decreased the diameter and strength of the aortic wall[27].

Based on those studied, it seems possible if we recommend patients with MS take low-moderate intensity exercise. Patients with MS should maintain HR <110 bpm or <100 bpm if on beta-blocker during exercise and monitor SBP ≤160 mmHg to avoid aortic dissection[24].

Time

Lack of study suggesting exercises duration in MS. However, the Marfan Foundation recommends taking 30 minutes at a time. Three 10-minute sessions are as effective as one 30 minutes session. It would be better to do some activities than none.

Physical activities routine is necessary to control BP, reduce some metabolic diseases, improving the cardiovascular system at the same time. However, there is an adjustment in duration among people with MS due to organ system involvement and complication severity[24].

Malek et al. designed a 12 weeks program with 20-60 minutes every session (3 times/week). From this point on, the patients will start a rehabilitation program with initially three sessions of 30 minutes of exercise, extended by 10 minutes every two weeks until 60 minutes and with intensity increased appropriately to set the targets (55-65% of maximal HR and/or SBP ≤160 mmHg). This study program design has been submitted but not validated yet[21].

Based on published data, we recommend exercising regularly for 30 minutes per session. This outcome should increase patients' physical activity with all of the benefits of healthy while maintaining safety and close monitoring.

Type

Patients with MS are followed to encourage non-competitive, isokinetic nonstrenuous aerobic activities. Avoid activities involving isometric work such as weightlifting, climbing, gymnastics, pull-ups, and activities involving rapid pressure changes[35]. AHA/ACC Aortic Guidelines (2010) also recommend avoiding collision sports and strenuous activities requiring Valsava for patients with TAD[36]. Penington et al. also suggested doing multiple repetitions at low resistance instead of a few repetitions with a heavyweight[35].

Strenuous and isometric exercise might cause aortic dissections in TAD patients[30]. According to Bethesda Guidelines for Marfan Syndrome (2015), patients with MS may participate in low-moderate static/low dynamic competitive sport with under condition no evidence of aortic root dilatation >4.0 cm in adults or 2 SD from the mean for BSA in children, moderate-severe MR, family history of dissection in a Marfan relative. The other exercise recommendation among the various organisations, ESC, AHA/ACC, and the Marfan Foundation, recommend to avoid isometric exercise, collision and strenuous activities (push up, lifting, straining), and contact sport[24,37,38].

The latest study from Uchida et al. described that 1 to 31 cases of TAA dissection occur during sports activities. That 49 patients suffered from Stanford type A (42 patients) and Standford type B (7 patients) dissections[39]. The primary cause is associated with weightlifting[40]. Benninghoven et al. implemented an observational study to inpatient a 3-week rehabilitation program for 17 Marfan patients and 1 Loeys-Dietz patient. All participants start the dynamic physical training then monitor for HR and BP. It showed improving physical fitness and psychological well-being within three weeks of programs. However, this study still has many limitations. No measurement of aortic changes and lack of participans[32].

It is important to know what exercise type is safe for Marfan patients to distinguish between dynamic/isotonic and static/isometric since both initiate different hemodynamic responses. Based on published data, we recommend that patients with Marfan do dynamic exercise and avoid isometric, strenuous exercises (such as weightlifting, gymnastics, push-up) and contact sports. It is supported by Mas-Starchurska et al. that dynamic exercise in moderate-intensity can prevent dilatation of aortic root and reduce cardiac hypertrophy in Marfan's mice[22].

Based on the FITT explanation above, we recommend the prescription as seen in Table V.

Conclusion

MS is an inherited autosomal dominant disease involving connective tissue. MS has many clinical manifestations. The most important and most life-threatening manifestation is aortic dissection. In addition to pharmacological/surgical therapy, rehabilitation also has an essential role in improving the quality of life, slowing the deterioration of the condition, and increasing the patient's functional capacity.

Exercise rehabilitation already has sufficient shreds of evidence to provide benefits for cardiac manifes-

Table IV: Following table lists of METs values for some activities based on intensity[24].

Light < 3,0 METs	Moderate 3,0 – 6,0 METs	Vigorous >6,0 METs
- Walking (leisurely) - Sitting (desk work) - Light housework (dishes, sweeping) - Fishing - Playing a musical - Instrument - Gardening (light) - Golf (with cart) - Boating - Bowling	- Walking (briskly—4 mph) - Heavy cleaning (mopping, vacuuming) - Mowing lawn (using power mower) - Bicycling (leisurely pace—10-12 mph) - Dancing (leisurely pace—ballroom) - Badminton (leisurely) - Golf (pull cart, walking) - Doubles tennis (leisurely) - Yoga - Pilates - Water aerobics (leisurely) - Swimming (recreational, light) - Calisthenics (light, without weights) - Hunting - Raking lawn	- Hiking (moderately up, steep grade) - Jogging Moderately (6 Mph) - Shoveling - Farming (bailing hay) - Singles Tennis - Basketball - Soccer - Bicycling At A Fast Pace (14-16 Mph) - Swimming (fast)

Table V: Exercise prescription for Marfan Syndrome patients.

	Prescription
Frequency	4-5 times/week
Intensity	Low to Moderate intensity Always monitor HR <110 or <100 if on beta-blocker monitoring SBP ≤160 mmHg
Time	Regularly for 30 minutes per session
Type	Dynamic exercise

tations of Marfan's patient. The exercise prescription use FITT methods will make the doctor easier to advise regarding safe exercise for Marfan's patient. Regular exercise in dynamic low-moderate intensity for 30 minutes in 4-5 times/week has significantly beneficial related to reducing aortic dilatation leading to aortic dissection and improving physical and emotional well-being.

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