Haemophilia and Exercise

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Haemophilia and Exercise

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- resistance training
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Abstract

One of the most important objectives of intervention programs for persons with haemophilia (PWH) is to improve their quality of life. Regular physical activity has been recommended as an adjunct to conventional treatment, with positive results in the prevention of joint problems and bleeding, in addition to the improvement in cardiovascular function, muscle strength, and body composition. The objective of the present review was to present the benefits of aerobic and resistance training programs in PWH, as well to discuss the best exercise dose-response in the different levels of disease severity. We considered randomized controlled trials, study cases and literature reviews from MEDLINE and Highwire databases. After a detailed analysis of the studies involving exercise for PWH, it can be concluded that this intervention elicits some benefits for physical fitness and blood coagulation mechanisms, suggesting the application of physical training as a non pharmacological treatment in association with conventional treatment. Adequate and periodized resistance training considering the disease severity, accompanied by physical education professionals could improve muscle strength, balance and proprioception. In addition, aerobic training could reduce the risks of obesity and several metabolic and cardiovascular diseases. Exercise can improve several outcomes of quality in PWH.

Introduction

Haemophilia is a hereditary disorder associated with a recessive trace in the X chromosome resulting in a deficiency in the coagulation factor VIII (i.e. haemophilia A) or factor IX (i.e. haemophilia B). Due to the variable bleeding phenotype of this disorder, the clinical picture ranges from life-threatening and traumatic bleeds to mild or no bleeding tendency [9]. In the most severe state this disease is characterized by severe chronic and recurrent bleeding that subsequently induces painful joint deformity [9]. Without treatment most people with haemophilia die.

The frequent musculoskeletal bleedings ongoing in persons with haemophilia (PWH) result in limitations and deficiencies of the musculoskeletal system, affecting the performance of daily living activities as compared with healthy individuals [25]. The clinical manifestations may include increased body temperature, pain, muscle atrophy, abnormal gait, weakness, haemarthrosis, reduced joint range of motion or even the development of degenerative alterations in joint. The damage resulting from haemarthrosis may cause periods of joint immobilization, tendon weakness, stiffness and joint destruction, a part from a decreased bone mineral density (BMD) associated with a higher risk of fractures and osteoporosis [3].

Prophylactic treatment with the use of coagulation factor is efficient in reducing bleeding episodes in PWH [16]. To improve quality of life in patients with haemophilia represents one of the most important objectives of health care programs. The deterioration of conditional and coordinative abilities is associated with the increased frequency of joint bleeding. Paradoxically, up to the beginning of the 70 s, physical activity was totally contra-indicated for this population, as it was considered an "unnecessary" risk [11]. In contrast, in order to avoid this vicious cycle, treatments with physiotherapy and physical activity are currently recommended [20, 25].

For PWH, regular physical activity is extremely relevant as it results in general and specific benefits, such as the increase in strength, flexibility, skeletal muscle cross-sectional area and decreased body fatness. Physical training also

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reduces the risk of development of several diseases, increases BMD, improves self-image, cardiovascular fitness, joint stabilization and coordination [11,22]. On the other hand, hematologic aspects may also improve by a decrease in the number of circulating inflammatory cells, reducing or preventing bleeds of the skeletal-muscle system [11,22,23]. However, the optimal dose-response for exercise prescription for PWH has not been well addressed. Thus, the aim of the present review was to analyze the benefits of exercise for PWH with emphasis on physical training prescription and the level of severity of the patients.

Haemophilia

Haemophilia is a rare genetic autoimmune and hereditary disorder, localized in the X chromosome, which causes the decrease or absent of blood coagulation factors – factor VIII (FVIII) and factor IX (FIX) for haemophilia A and B, respectively. This disorder causes bleedings as a result of a damaged blood vessel, since that a blood clot is not formed and the bleeding persist [15]. The overall prevalence of haemophilia is usually estimated at 1:5 000 million people/year [14], being type A the most common, with 90 % of the total cases [28].

In 1900, life expectancy was 11.3 years; while currently is about 60–70 years [13]. This increase is in part due to the prophylactic treatment with intravenous administration of coagulation factors VIII and IX (FVIII and FIX), in order to maintain the values above 1 % [16], which may avoid or suspend bleeds. However, up to 1/3 of the patients develop an inhibitor antibody against the coagulation factor, turning it inactive and ineffective, while intravenous administration may induce a certain tolerance [17].

Haemophilia severity may be classified according to the levels of deficiency in coagulation factors [15]:

- Mild: coagulation factor between 5–40 %. It is rarely associated with spontaneous bleedings.
- Moderate: coagulation factor between 1–5 %.
- Severe haemophilia: coagulation factor is lower than 1 %.

Although world prevalence of the disease is low as reported on the Annual Global Survey Report of 2009 [26] with for example 16,667 cases in The United States of America and 10,026 cases in Brazil (n = 10 026), it should be pointed out that treatment costs are high. Therefore, this reinforces the necessity of costless and accessible alternative therapies, such as regular physical activity and exercise.

Methods

We performed a review of literature on physical training in PWH considering randomized intervention studies, case reports and review articles. The search started with the election of the terms in the fields of treatment and exercise in PWH; that is, "haemophilia" plus "exercise" (n = 983), or "quality of life" (n = 776), or "rehabilitation" (n = 539), or "resistance training" (n = 15), or "aerobic training" (n = 8). The databases selected for searching were Highwire and Medline. The articles should be written in English language and with no more of 30 years since their publication. An additional criterion for inclusion of intervention studies was a precise and detailed description of the methodology, specifically with respect to the load of the training program. In this regard, studies that did not show a clear association between exercise and haemophilia from a dose-response perspective were excluded. Thus, studies that did not include the description of the level of severity of the PWH could not be considered. After the application of these filter criteria, only 8 studies were subsequently included on this review to discuss exercise dose-response (see ▶ **Table 1** for a detailed description). This does not exclude the employment of other related studies for a more appropriated discussion in this work.

Exercise in haemophilia

Because of the frequent musculoskeletal bleeds, PWH limit their physical activities early in their life, thus developing physiological, neurological, and functional disorders as a consequence of their sedentary lifestyle [21]. From that, it may be suggested that exercise is an appropriate preventive tool for PWH. For example, it should be noted that proprioception is important in the sense that it helps afferent information from intra-joint receptors which are affected by repeated joint bleeding [12]. In this regard, it has been demonstrated that PWH could be strongly benefitted with improvements in muscle strength, balance and proprioception capacities [4,5,10].

PWH could benefit from physical training by: lowering the risk of metabolic illness, obesity, diabetes, cardiac and vascular problems [24], diminishing the incidence of degenerative chronic disorders, osteoporosis, arthropathy, and intramuscular or joint bleeding [4,10]. Furthermore, acute exercise sessions increment the levels of Factor VIII, subsequently improving coagulation in mild patients [14]. Given the sparse and non-conclusive evidence on this issue, additional studies with larger samples and special attention to the dose-response of the different exercises are warranted.

Special care in physical training prescription for PWH

Given the potential complications derived from this pathology during physical training, some care [10,18] should be taken before starting a training program with PWH:

1. To obtain medical permission for physical training depending upon the level of severity.
2. Evaluation by a physiotherapist or a physical trainer for determining the functional capacity of the patient for a more individualized training prescription.
3. Before starting the program, it is interesting to evaluate the level of joint range of motion limitations for determining the range of secure movement.
4. To have coagulation medication available for potential light-to-moderate bleeds.
5. To use prophylactic coagulation factor for severe bleeding disorders, including the time before exercise sessions if needed.
6. To execute the exercise without pain.
7. To employ the estimated maximum heart rate because of the biomechanical limitations exhibited before the maximum heart rate is achieved in an incremental test.
8. Because of the joint limitations in PWH, stretching after an active warm-up may be suggested.
9. To avoid activities with some form of biomechanical stress like impact or shear stress.
10. The periodization and the achievement of the objectives should be considered in the long-term.

Haemostasis and exercise

A potentially important but conflicting issue is the effect of exercise on coagulation parameters. Paradoxically, this topic has received little attention in PWH while it has been intensely

Table 1 Summary of the interventions with exercise.

Author	Number of patients	Intervention duration	Training/Intensity	Weekly frequency	Severity of haemophilia	Results after the intervention
Broderick et al.[4]	35 children	12 weeks	Treadmill (60–70 % estimated HRmax) – moderate intensity	2x/week 30 min	Mild, moderate and severe	Unconcluded study
Broderick et al.[4]	35 children	12 weeks	Resistance training (3× 8–12 RM) –moderate intensity	2x/week 20 min	Mild, moderate and severe	Unconcluded study
Hill et al.[12]	20 adults	16 weeks	Walking (moderate intensity)	5–7x/week	14 severe, 5 moderate and 1 light	Improvement in some balance parameters
Vallejo et al.[24]	13 adults	9 weeks	Aquatic exercise (50–70 % estimated HRmax) – light to moderate intensity	3x/week 20 min	12 severe and 1 moderade	Increase in VO_2 (51,5 %) and improved mechanical capacity (14,7 %)
Mulvany et al.[18]	33 (7–57 yr)	6 weeks	Aquatic and ground treadmill (50–70 % estimated HRmax) – light to moderate intensity	2x/week 20 min	Mild, moderate and severe	Increase in strength, improved joint range of motion, increase of distance in the 6 min walk test
Mulvany et al.[18]	33 (7–57 yr)	6 weeks	Resistance training – 1 exercise per muscle group (1 × 10 repetitions at 40 % MIF for level 1 and 2; and level 3: 1 × 10–20 repetitions at 60 %MIF reaching 70 %) associated with proprioception exercises.	2x/week 20 min	Mild, moderade and severe	Increase in strength, improved joint range of motion, increase of distance in the 6 min walk test
Tiktinsky et al.[23]	2 previously active adults (karate and swimming)	1 and 2 years	Resistance exercise – Bench press and Leg press (3 × 12–15 or 3 × 4–8 submaximal repetitions) – moderate intensity and stretching for large muscle groups	3–5x/week 30–45 min	Severe	Increase in strength, decrease in the bleeding episodes (from 2–4x/month to none or almost none)
Hill et al.[12]	20 adults	16 weeks	Resistance training for lower limb – moderate intensity, associated with exercises for proprioception	5–7x/week	Mild and moderade	Increase in lean body mass
Hilberg et al.[11]	28 adults	6 months	20–25 repetitions with therabands for stabilizer muscles of the trunk and lower limb – light intensity	2x/week 120 min	Severe	Increase in lean body mass, strength and proprioception of the lower limb
Pelletier, Findley and Gemma[20]	Case study	3 weeks	10 repetitions for 10 s–Extension/flexion knee exercises at 45, 60 e 90 degrees with a tensiometer – intensity: 2/3 (20 % of the maximal voluntary isometric contraction), associated with proprioception exercises.	3x/week 20 min	Severe	Increase in strength and proprioception of the lower limb

Abbreviations: MIF = maximal isometric force; RM = repetitions maximum; HRmax = maximal heart rate studied in healthy people and other pathologies although with contradictory results [5]. Moreover, it should be pointed out that the complexity of the haemostatic cascade, with some factors influencing simultaneously on various steps on the coagulatory and the fibrinolytic processes, do not allow a mechanistic approach to the problem. In this regard, it is not known if the same mechanisms could be expected in both healthy people and in PWH. Furthermore, another important limitation refers to the wide methodological variations of the studies, including differences in exercise programs, population's characteristics and the analytical methods employed for the determination of haemostatic indices [5].

For instance, the effects of acute aerobic exercise (10 min of walking) on thromboelastography pattern (TGE) and complete hemogram have been tested in 23 dogs with severe haemophilia (<1% of FVIII) [19]. TGE was used to evaluate body haemostasis, while hemogram served to evaluate changes in hemoglobin and platelets. There was a significant improvement in global haemostasis after exercise, detected by the increase in FVIII activity, decrease in the mean time of coagulation (18.6%) as compared with pre-exercise (15 min versus 12 min), apart from the 26% elevation in platelets [19]. In humans, it has been shown that an acute submaximal exercise performed on a cycloergometer, reduced the time of production of a coagulation factor (i.e. prothrombin time, from 11.7 to 11.2 s) in 11 patients with moderate and severe haemophilia, while the levels of coagulation factors II and VII increased [14]. On the other hand, others [2] observed that coagulation factors increased only after high intensity exercise in healthy men. Although the above mentioned results are promising, more information is required. Thus, more research with a higher number of patients is needed and, more importantly, with regard to the chronic effect of exercise on haemostasis.

Aerobic training in haemophilics

Considering the above mentioned limitations, it can be understood why haemophilics become sedentary. Thus, a decrease in aerobic capacity is normal in PWH compared with normal individuals. This deleterious phenomenon is a result of excessive protection by parents regarding mechanical limitations in the early infancy [6]. As a consequence, movement possibilities are reduced, mainly by pain that is reached even before ventilatory threshold (moderate intensity, ratings of perceived exertion ~13/14; 70–85% of maximum heart rate). Another relevant issue is the fact that treadmill with incremental loads and inclination cause additional stress in the lower limb joints, which are usually already affected. Also during testing on the cycloergometer, some patients may exhibit a limited angle of knee flexion. In this sense, submaximal parameters should be used in the determination of cardiorespiratory capacity and prescription of exercise intensity in PWH [10, 24].

By using a test to determine maximal and submaximal aerobic parameters on the treadmill, some authors [10] compared 11 severe haemophilics with 11 healthy individuals aged 16–44 yr. The test used was developed for patients with heart failure, starting at 3 km/h, progressing to 6 km/h, and later, increments of 2.5% in inclination every 3 min, ending whenever the patient felt pain or muscle fatigue. VO_2 (oxygen consumption), VCO_2 (carbon dioxide production), VE (ventilation), RER (respiratory exchange ratio), RF (respiratory frequency) and HR (heart rate) were determined. Blood lactate was measured before, during and after the test. Only 6 of the 11 haemophilics reached 6 km/h at 10% of inclination; while in 4 of them knee and ankle joints were severely affected; the remaining 3 were not affected. The authors concluded that PWH presented an aerobic deficit in maximal parameters (14–16% lower than healthy individuals), and in submaximal (30% lower power at the individual anaerobic threshold). Additionally, haemophilics had a decreased endurance performance, while anaerobic threshold was reached at 147 W compared with 210 W for normal individuals. The conclusions from this study should be critically analyzed, as only 11 individuals with haemophilia aged 16–44 yr were tested. Thus, these results cannot be applied for the mild and moderate levels of the disease.

Low aerobic capacity generates unfavourable metabolic conditions and increases risk factors for cardiovascular disease and lower expression of key proteins necessary for optimal mitochondrial function. A blunted regulation of oxidative pathways is possibly associated with a decreased aerobic capacity, which also increases the risk of obesity and cardiovascular disease in PWH [27].

There was a significant increase of 51.51% in VO_2 during the Cooper test after an aquatic aerobic training in 13 adults (age 32.17 yr) with moderate and severe haemophilia [24]. The training protocol consisted of 9 weeks, 3 times per week, 1 h of duration with 20 min of aerobic training at an intensity set at 50–75% of the estimated HRmax. Considering that patients with severe haemophilia present a decrease in aerobic capacity, only 9 weeks of aerobic training in previously sedentary individuals can improve their aerobic capacity.

Others [18] investigated the efficiency and safety of several types of aerobic exercise for people with mild, moderate and severe hemophilia (33 patients aged 7–57 yr) during 6 months of intervention. Specifically, they aimed to investigate which exercises allowed haemophilics to reach 20 min of continuous exercise. In this study, aquatic treadmill, hydrotherapy, treadmill and aerobic gymnastics of low intensity were used. The authors concluded that aquatic exercise resulted in a better effect in those individuals with higher limitation in joint range of motion. According to this study, cycloergometer is not advised for this type of patient, as haemophilics present difficulties in movement, caused by a restriction in joint range of motion, pain and discomfort.

In this previous study [18], an intensity corresponding to 50% of estimated HRmax was used in the first 2 weeks, progressing to 5–10% in the following sessions up to 70%, in the absence of adverse effects. Although only 61% of the patients completed the study (transportation problems, commitments and diseases), while there were no clinical issues during the study. Unfortunately, some study limitations need to be addressed such as the duration of the intervention (only 6 weeks), a reduced number of patients with concomitant diseases (common in this population), age discrepancies and presence of the same evaluator in all analysis.

Considering the limitations in selecting patients with haemophilia as presented in the studies previously conducted [10, 18], it is possible to conclude that aquatic aerobic exercise is an important tool for haemophilics with higher limitations in joint range of motion, especially those being sedentary at the beginning of an exercise program. In this sense, the extent to which osteomuscular and physiological adaptations occur, as well as medical release, ground aerobic exercise should be considered. It is important to express that these recommendations are only guidelines to facilitate an exercise program prescription and should not be considered as fixed rules.

Others [12] suggested the appropriateness of a specific exercise program with a minimal duration of 4 months consisting of walking, proprioception and muscle strengthening. According to the authors this type of exercise program induces positive results, including improvements in balance and mobility in patients with moderate and severe haemophilia. Similarly to a previous study [18], ~60% of participants completed the training, while none of them stopped the program due to adverse effects of exercise. Again, aerobic exercise performed in water was positive for type A haemophilics, improving aerobic and mechanical capacity, without adverse effects [24]. Interestingly, regarding pain, it may be suggested that the increase in endorphin plasma levels in response to aerobic exercise could be possibly one of the mechanisms responsible for joint pain decrease [23].

In summary, although some studies found an increase in coagulation factors after acute aerobic exercise, the exact intensity remains uncertain. Thus, the dose-response for aerobic exercise prescription requires further clarification. Moderate intensity set at 50–70% of estimated HRmax, used in majority of the studies seems to be safe, which may avoid possible joint problems and induce an increase in cardiorespiratory capacity. Aerobic exercise associated with resistance training can improve functional capacity and joint range of motion. However, the target intensity to elicit an elevation of coagulation factors remains to be determined. ▸ **Table 1** presents a brief description of the main studies with aerobic exercise, as well as the respective intensities used.

Resistance training for PWH

Haemophilia promotes atrophy because of the inherent inactivity of this condition, leading to the weakness of muscles and joints thus lowering their stability and incrementing the probabilities of new injuries. This process increments the probability of falls and subsequently the worsening of the synovitis, therefore increasing bleeding episodes and the occurrence of new injuries, thus causing a vicious circle. Besides this, muscle strength has been demonstrated to highly correlate with the capacity for performing activities in daily life [1]. In this regard, some authors [7] suggested the necessity of resistance training for children with haemophilia as they have demonstrated lower levels of anaerobic capacity and strength when compared with children without haemophilia. Resistance training may be a proper exercise mode for PWH because it is safe, free of impacts, collisions and falls, improves strength and proprioception, diminishes pain and bleeding occurrence and promotes the increment of the bone mineral density [4].

Resistance training with concentric and eccentric muscular actions

Some authors [23] have previously applied dynamic exercises in 2 adult PWH and reported muscular strength improvements and joint range of motion; and a reduction in the occurrence of bleeding with a concurrent pain lowering that could be due to the increment on movement amplitude that accompanied the gain in strength. Therefore, this study reinforces the importance of resistance training for PWH, not only because of the strength gains but also because of the reduction in the episodes of bleeding and associated pain. Therefore, low-intensity resistance training (e.g. 20–25 repetitions) could increment proprioceptive capacity with a minimum effort and stress for the joints. Besides this, the limited number of participants of this study limits the extrapolation of the results for all the levels of severity in haemophilia.

Others [18] performed a study with classical periodization (i.e. incremental load) with one exercise per muscle group during 6 weeks in PWH (33 patients aged 7–57 yr). A hand-held dynamometer was utilized for maximal isometric force (MIF) determination. For level 1 of PWH, they prescribed 1 set of 10 repetitions at 40% of MIF for those target joints previously determined as injured. For level 2, physical training was prescribed on those joints with previous bleeding and arthropathy, but without bleeding during the previous 6 months. For this level, exercise consisted of 1 set of 10 repetitions at 50% of MIF. Regarding the level 3, exercise prescription for the first week was made for those muscle groups and joints that did not exhibit any damage, with 1 set of 10–20 repetitions at 60% MIF. During the 2 following weeks a set was added for every week and then the intensity was incremented progressively up to 75% of MIF, while the patient did not experience any pain or swelling. It is interesting to note the suggestion of "therabands" use in those patients experiencing any pain, discomfort or limitation in the employment of free weights or machines. The results of this study suggested an improvement in muscle strength, range of motion and in the distance covered in the 6 min walk test with the consideration of some limitations as previously suggested.

Given the limited number of studies with resistance training and the absence of strong guidelines with regard to the level of joint bleedings, the training load of this previous study [18] would be considered the best option for resistance training prescription in this population. This is true because this work considered the level of severity with respect to joint bleedings and injuries. Additionally, the patients of this study did not exhibit any collateral effect of training with a good tolerance reported in this model of intervention. A detailed summarize is also presented in ▸ **Table 1** with reference to the training load employed.

In summary, resistance training, alone or combined with aerobic training, may increment muscle mass and strength, joint range of motion, and the proprioception of the lower limbs and therefore functional capacity; with a reduction of the bleeding episodes and pain in PWH. These benefits would suggest the recommendation of resistance training in water, with "therabands" or free weights, considering the severity of the disease. Further studies should be conducted for determining if PWH could perform resistance training in the same range of intensities as for healthy people.

Isometric training in PWH

Isometric training (IT) is a modality of strength training in which there is no change in muscle length [8]. Others [20] suggested that it could be a safe and effective training modality in PWH because of its lower injury risk, allowing IT applicability in the most acute phases of the disease. Moreover, low intensity IT leads to significant muscle strength improvements minimizing the local trauma and thus the necessity of more severe therapies. These authors reported an improvement of about 40–70% in muscle strength after 3 weeks of IT that consisted of 10 repetitions of 10 s on a tensiometer. Additionally, the authors recommended IT as a promising treatment for PWH for both fitness maintenance and rehabilitation.

Conclusions

After a detailed review on the studies using exercise as a therapeutic tool for people with haemophilia, it can be concluded that this intervention induces several benefits on physical fitness and coagulation factors. Therefore, exercise may be used as a preventive therapy, associated with medication, considerably attenuating the disorders caused by haemophilia.

The combination of aerobic and resistance exercise may be an optimal election for the improvement of physical function. Whenever prescribing resistance training, a high number of exercises and elevated load is not necessary. It is important to note that more randomized controlled studies with a higher number of individuals are necessary to address the dose-response of exercise in PWH.

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