



### Effect of Water Exercise on Atrophic Muscles Associated with Limited Range of Motion in Severe Haemophilia A Patients: a Pilot Study

Şiddetli Hemofili A Hastalarında Sınırlanmış Eklem Açıklığı ile İlişkili Atrofik Kaslarda Su İçi Egzersizlerin Etkisi: Bir Pilot Çalışma

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#### ABSTRACT

**Purpose:** Haemophilia causes musculoskeletal problems over many years secondary to recurrent hemarthrosis. In this study, the effects of water exercises on the musculoskeletal system of severe haemophilia A patients with muscle and joint problems were investigated.

**Material and Methods:** Eleven severe haemophilia A patients on prophylaxis treatment participated in the study and following a regular exercise protocol.

**Results:** Subjects displayed statistically significant increases in mid-thigh, upper thigh and calf circumference for right leg ( $42.0 \pm 2.4$ ,  $43.0 \pm 2.1$  ;  $37.1 \pm 1.9$ ,  $39.0 \pm 1.8$ ;  $28.1 \pm 1.4$ ,  $28.9 \pm 1.3$  respectively) (mean  $\pm$  SE) in mid-thigh and upper thigh for left leg ( $36.9 \pm 1.5$  ,  $38.9 \pm 1.5$  ;  $41.2 \pm 2.2$  ,  $42.9 \pm 2$ ) ( $p < 0.05$ ). Compared to pre-exercise values, leg extensor and flexor strength as well as range of motion were increased significantly ( $96.6 \pm 9^\circ$  vs  $104.5 \pm 8^\circ$ ; before and after training for right knee,  $98.5 \pm 7.6^\circ$  vs  $104 \pm 7.9^\circ$  before and after training for left leg respectively) ( $p < 0.05$ ). In addition to that, post training serum level of growth hormone was found to be significantly higher than the pertaining value ( $p < 0.05$ ).

**Conclusion:** These results show that some easily performed exercise protocols such as water exercises can promote muscle development and increase range of motion of the knee joint. Our findings indicate that appropriately designed water exercise may prevent muscle atrophy and joint deformities in haemophilic patients.

**Key Words:** Haemophilia, Water exercise, Muscle atrophy, Muscle strength.

#### ÖZET

**Amaç:** Hemofili tekrarlayan kanama ataklarına sekonder olarak kas- iskelet sorunlarına neden olmaktadır. Bu çalışmada, su içi egzersizlerinin, kas ve eklem problemleri olan şiddetli hemofili A hastalarında etkilerinin araştırılması amaçlanmıştır.

**Materyal ve Metod:** Profeksi alan, şiddetli hemofili A hastası (n=11) düzenli olarak egzersiz uygulamasına alınmıştır.

**Bulgular:** Çalışmaya katılan hastaların, sağ bacaklarında üst bacak, orta bacak ve calf çevrelerinde ( $42.0 \pm 2.4$ ,  $43.0 \pm 2.1$  ;  $37.1 \pm 1.9$ ,  $39.0 \pm 1.8$ ;  $28.1 \pm 1.4$ ,  $28.9 \pm 1.3$  respectively) (mean  $\pm$  SE), sol bacaklarında üst ve orta bacak çevrelerinde ( $36.9 \pm 1.5$  ,  $38.9 \pm 1.5$  ;  $41.2 \pm 2.2$  ,  $42.9 \pm 2$ ) egzersiz öncesi değerlerine göre istatistiksel olarak anlamlı

farklılık bulunmuştur ( $p < 0.05$ ). Egzersiz öncesi değerlerle karşılaştırıldığında ekstensör ve fleksör kuvvetlerde olduğu gibi eklem hareket açıklığı (ROM) da anlamlı olarak artmıştır. (Sağ diz için ROM ( $96.6 \pm 9^\circ$ ,  $104.5 \pm 8^\circ$ ; sol diz için  $98.5 \pm 7.6^\circ$ ,  $104 \pm 7.9^\circ$ ) İlaveten, büyüme hormonu egzersiz sonrası değerleri, öncesine göre anlamlı olarak bulunmuştur. ( $p < 0.05$ )

**Tartışma:** Bu sonuçlar bize, su içi egzersizler gibi kolayca yapılabilecek egzersizlerin diz eklem hareket açıklığını ve kas kuvvetini arttırabileceğini göstermektedir. Bulgularımız göstermektedir ki, uygun olarak düzenlenmiş su içi egzersizler hemofili hastalarında kas atrofisi ve eklem deformitelerini önleyebilir.

**Anahtar Kelimeler:** Hemofili, su içi egzersizi, kas atrofisi, kas kuvveti

## INTRODUCTION

The common problems that haemophilia patients encounter are hemarthrosis and attacks of synovitis<sup>1</sup>. Daily physical activity following an acute bleeding episode may cause serious musculoskeletal problems. Edema and joint pain may affect joints and limit their range of motion (ROM). The blood resorbed after the first bleed accumulates in articular structure and as bleeds occur more frequently, the residual blood contributes to the development of inflammation<sup>2,3</sup>. In this situation, a joint may bleed more easily, while the resultant pain increases immobility and a vicious cycle may be established. Atrophy and loss of muscle strength may chronically occur disuse of the muscles surrounding the joint. Damage to the joints develops because of synovitis attacks and induce joint damage and reduction of ROM in the chronic period promotes joint deformities<sup>1,2,3,4</sup>. The knees, elbows, shoulders and ankles which are the most affected joints. However the problems with in the knees are worse than with any other joints because of accumulated damage. Muscle atrophy and loss of strength were among the problems encountered in later stages of the disorder. Today, based on the guideline determined by the World Federation of Hemophilia, patients are encourage to increase muscle strength and protect range of motion<sup>4,5,6,9</sup>. Water exercise is the most highly recommended sport for haemophilic patients in their daily life<sup>8</sup>. During physical activity the joints are supported by the surrounding water, that make exercise much easier and safer compared to when they are performed on dry<sup>10,11,12,13</sup>. Although

the resistance of water is much higher than atmosphere. Possibility of contact or impact in water is minimal<sup>9,12</sup>.

The signaling pathways that lead to muscle hypertrophy as a result of exercise have been studied in details<sup>22</sup>. However, the ability of water exercises to increase muscle strength in haemophilia patients is unknown. The increase in plasma growth hormone, which may be associated with increased muscle strength after exercise, may contribute to this response<sup>15,16</sup>. The effect of simple and basic water exercises on the level of this hormone is unknown for hemophilic patients

With this in mind we aimed to study the effects of water exercise on atrophic muscles associated with limited range of motion in severe haemophilia A patients with knee damage from previous bleeds.

## MATERIALS and METHODS

Eleven severe haemophilia A patients between the ages of 6 and 24 years who were deemed appropriate to perform water exercises by the Cukurova University Faculty of Medicine, Department of Pediatric Hematology, participated in this study. All patient received prophylactic replacement therapy as 25-40 iv/kg two times per week. All procedures were explained to the patients and/or their families in detail before entering the study and all patients signed a consent form, as confirmed by the Ethics Committee of Cukurova University, Faculty of Medicine.

Before starting the exercise program their body weights and heights were measured on electronic scale (Sport Expert, Turkey). Inelastic tape was used to measure circumferential diameters of the ankle, calf, below-patella, patella, above-patella, mid-thigh and upper thigh. Tape was placed around the minimum circumference of the calf, perpendicular to its long axis, just proximal to the malleoli to measure ankle circumferences. Maximum circumference in a plane perpendicular to the long axis of the calf measured as calf circumferences. Upper thigh circumference was measured just under to the gluteal furrow. Midthigh circumference was measured at the midpoint of the inguinal crease and proximal border of patella. Measurements were performed by the same investigator through this study.

Digital goniometer was used for determination of knee joint range of motion (ME 3000, MegaWin, Finland). One end of goniometer was placed on the caput fibula and the other end on the lateral femoral epicondyle to determine the knee joint's passive range of motion. After the goniometer was positioned, the patient who was lying supine, flexed his knee joint from full extension while keeping his the soles of the feet on the floor. The patient then brought his knee to full extension while at rest. This procedure was repeated three times and the best angle obtained was accepted as ROM for the study data.

Muscle strength was measured by using the isometric module of an isokinetic dynamometer (NORM 6000 CSMI, USA). Before the measurement, the patient was secured in a chair with waist and chest belts in a 90° angle sitting position. The patient's leg was fixed to the dynamometer arm with a pad and connections were placed on his ankle. Isometric muscle strength was measured at 45° or 20° for knee joints according to the previously determined passive ROM values of patients (20° was used for patients with a knee extension angle less than 50° and 45° was used for patients with a knee extension angle over 50°). Isokinetic muscle force

measurements were performed at the same angle after training session. During this measurement, patients were requested to contract their leg extensor muscles for 15 seconds at maximal strength and this maneuver was repeated after resting for 20 seconds and the best value was accepted as muscle strength. Patients rested for another 20 second minute for flexor muscle strength measurement. Identical extensor strength measurement protocol was used muscle strength evaluation. These measurements were taken at the end of the study to evaluate the effect of the water exercises.

Blood samples were taken before the first training of this study. After completing two months of an exercise program following the final water exercise, blood samples were withdrawn within the 20-minutes period. Whole blood was centrifuged at 3500 rpm for 5 minutes and was separated into serum and stored at -80°C. And samples were studied at the central laboratory of Cukurova University, Faculty of Medicine by the chemiluminescence method (Immolate 2000, USA).

Patients were asked to perform water exercises for one hour per day, three days per week, for a total of two months. The Cukurova University Ozdemir Sabancı Indoor Swimming Pool was used for the training. For safety reasons, all patients were asked to wear life vests, regardless of whether they were able to swim. During in-water training, the number of supervisors was arranged such that one supervisor was responsible for, at most, three patients at a time. During the first days of the two-month training regimen, patients were asked to perform special exercises to help them adapt to the water and water exercises. During this adaptation period, the main goal was to make the leg muscles work; patients were asked to swim by holding onto a swim board with both hands. After approximately three sessions, patients were able to perform the requested movements easily. The swim board was used in all exercise period. Tired patients were allowed to rest and then continued to

swim. Via verbal instructions, patients were requested to increase their swimming intensity during each session. Patients exercised barefoot during the first three weeks and used flippers during training in the next five weeks period to increase water resistance. The patients were swam only with underwater leg kicking according to their physical capacities.

#### Statistical analysis

The data are presented as the average  $\pm$  standard error. A paired *t*-test was performed to evaluate pre- and post-training data for all patients. The relation between two variables was evaluated by a Pearson correlation test. A *p*-value  $<0.05$  was accepted as statistically significant.

### RESULTS

Main findings of this study are regular water exercise increased the muscle strength together with some circumferential values of lower extremity

and improved knee ROM. Circumferential measurements were performed at both of the right and left extremities. The upper thigh( pretraining  $42.0 \pm 2.4$ cm, post training  $43.0 \pm 2.1$ cm) ; mid-thigh (pretraining  $37.1 \pm 1.9$ cm, posttraining  $39.0 \pm 1.8$  cm) and calf circumferences (pretraining  $28.1 \pm 1.4$ ,post training  $28.9 \pm 1.3$  ) increased significantly at the right leg (Table 1). However right leg circumferential value below patella, above patella and ankle level was not significantly different compare to pretraining value. On the other hand mid thigh (pretraining  $36.9 \pm 1.5$  cm,post training  $38.9 \pm 1.5$  cm), upper thigh (pretraining  $41.2 \pm 2.2$ cm, posttraining  $42.9 \pm 2$ cm) and patella (pretraining  $31 \pm 1.3$ , posttraining  $31.4 \pm 1.2$ ) circumflexes improvement significant for the left leg, changes of circumferential measurements from the left lower extremities below the patella, above patella calf and ankle not significant (Table 2).

**Table 1. Circumferential measurements(mean  $\pm$ SE)from the right lower extremity before and after completion of training period . \* ( $p<0.05$ ).Changes in midtight, uppertight and calf circumferences was significant.**

| Circumferential Measurements (cm) | Before Training | After raining    |
|-----------------------------------|-----------------|------------------|
| Patella                           | $30.9 \pm 1.4$  | $31.5 \pm 1.3$   |
| Above patella                     | $30.5 \pm 1.6$  | $31.3 \pm 1.5$   |
| Below patella                     | $27.9 \pm 1.5$  | $27.9 \pm 1.3$   |
| Mid-thigh                         | $37.1 \pm 1.9$  | $39.0 \pm 1.8$ * |
| Upper-thigh                       | $42.0 \pm 2,4$  | $43.0 \pm 2.1$ * |
| Calf                              | $28.1 \pm 1.4$  | $28.9 \pm 1.3$ * |
| Ankle                             | $19.5 \pm 0.8$  | $21.0 \pm 1.0$   |

**Table 2. Circumferential measurements(mean  $\pm$ SE)from the left lower extremity before and after completion of training period . \* ( $p<0.05$ ).Changes in midtight, uppertight and patella circumferences was significant.**

| Circumferential Measurements (cm) | Before Trainig | After Training   |
|-----------------------------------|----------------|------------------|
| Patella                           | $31.0 \pm 1.3$ | $31.4 \pm 1.2$ * |
| Above patella                     | $29.4 \pm 1.3$ | $30.3 \pm 1.3$   |
| Below patella                     | $27.9 \pm 1.3$ | $27.9 \pm 1.2$   |
| Mid-thigh                         | $36.9 \pm 1.5$ | $38.9 \pm 1.5$ * |
| Upper-thigh                       | $41.2 \pm 2.2$ | $42.9 \pm 2.0$ * |
| Calf                              | $28.0 \pm 1.2$ | $28.8 \pm 1.2$   |
| Ankle                             | $19.6 \pm 0.9$ | $21.0 \pm 0.9$   |

With the goniometric analysis that designed to evaluate the range of motion of each patient's knees, we found that range of motion is increased significantly after training compared to pre-training values. Right knee ROM value was measured as  $96.6 \pm 9^\circ$  vs  $104.5 \pm 8^\circ$ ; before and after training ( $p < 0.05$ ). Similar improvement recorded knee ROM as well ( $98.5 \pm 7.6^\circ$  vs  $104 \pm 7.9^\circ$  before and after training the respectively) ( $p < 0.05$ ).

Isometric muscle strength was increased significantly after training, which agreed with our findings concerning circumferential limb measurements after training. Pre-training isometric extension and flexion forces were correlated with mid-thigh circumferential measurement by  $r^2 = 0.81$  ( $p < 0.001$ ) and  $r^2 = 0.83$  ( $p < 0.001$ ) respectively. After training the correlation of isometric extension and flexion forces with mid-thigh circumference was significant  $r^2 = 0.79$  ( $p < 0.001$ ) and  $r^2 = 0.84$  ( $p < 0.001$ ) (Figure 1A-1B).

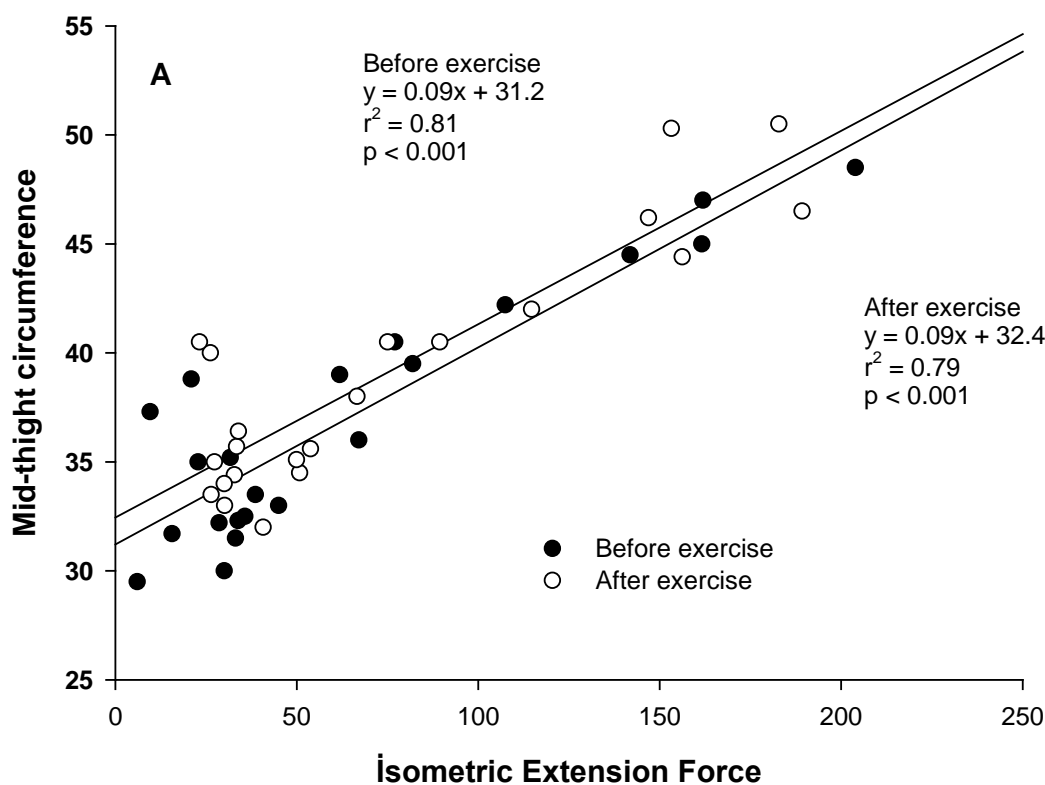
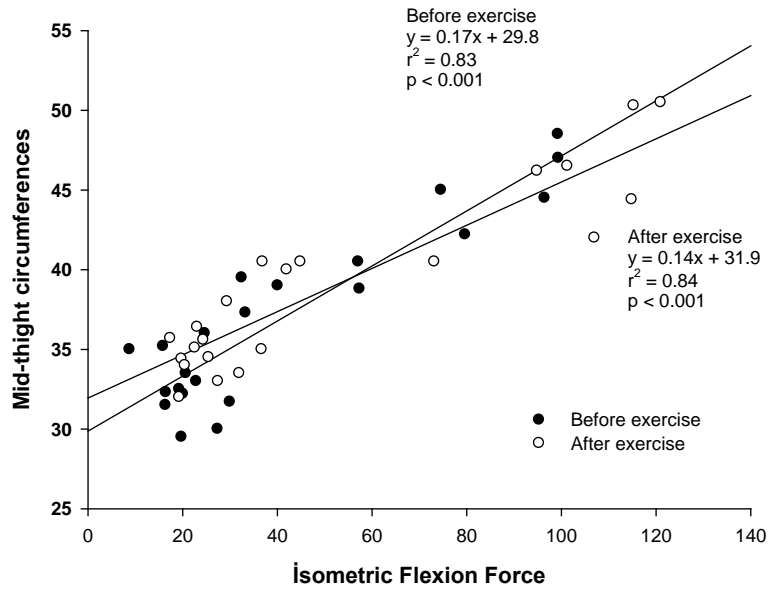


Figure 1A

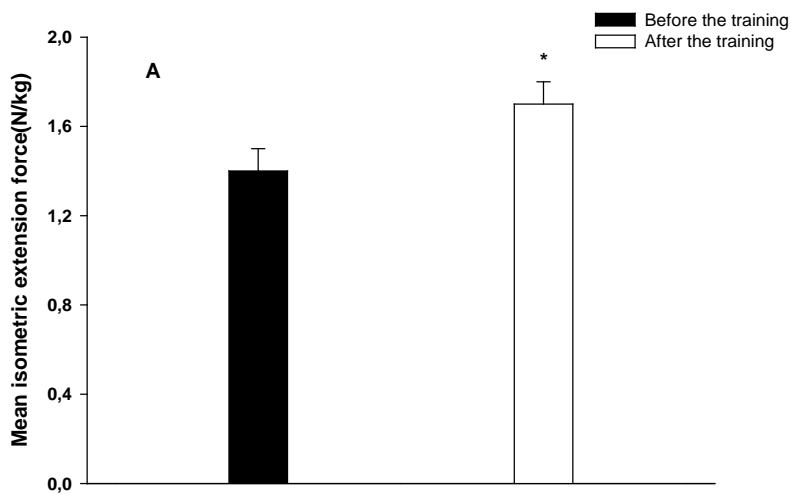


**Figure 1B**

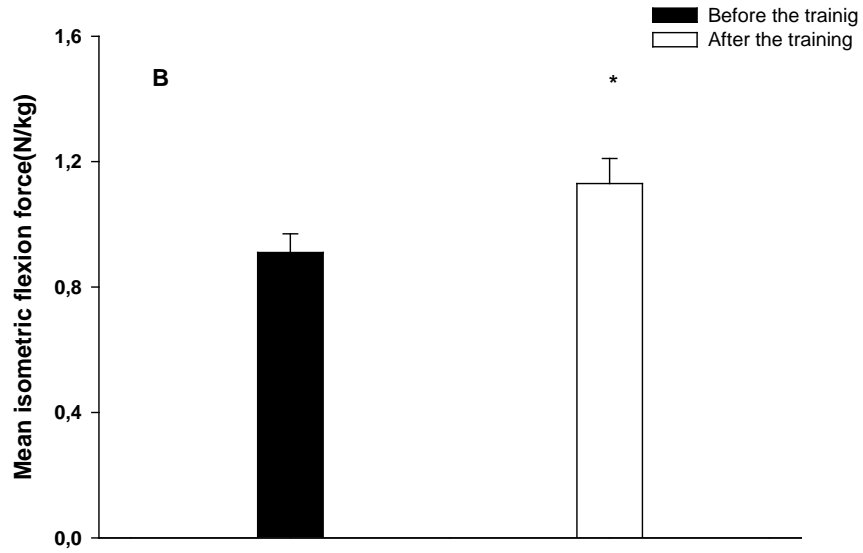
**Figure 1.**Correlation between midthigh circumferences with isometric extension force (A) and fleksion force (B) was found as significant for pretraining and posttraining.

Isometric torque values were evaluated for flexor and extensor muscle strength following body weight normalization. The initial mean extensor muscle strength was measured as  $1.4 \pm 0.1$  N/kg and training session improved the mean strength about % 21 ( $1.7 \pm 0.1$  N/kg after training) ( $p < 0.001$ )

(Figure 2A). Similar improvement was (~ %24) recorded between initial and final flexor muscle strength as well ( $0.91 \pm 0.06$  N/kg vs  $1.13 \pm 0.08$  N/kg for before and after training respectively) ( $p < 0.001$ ) (Figure 2B).



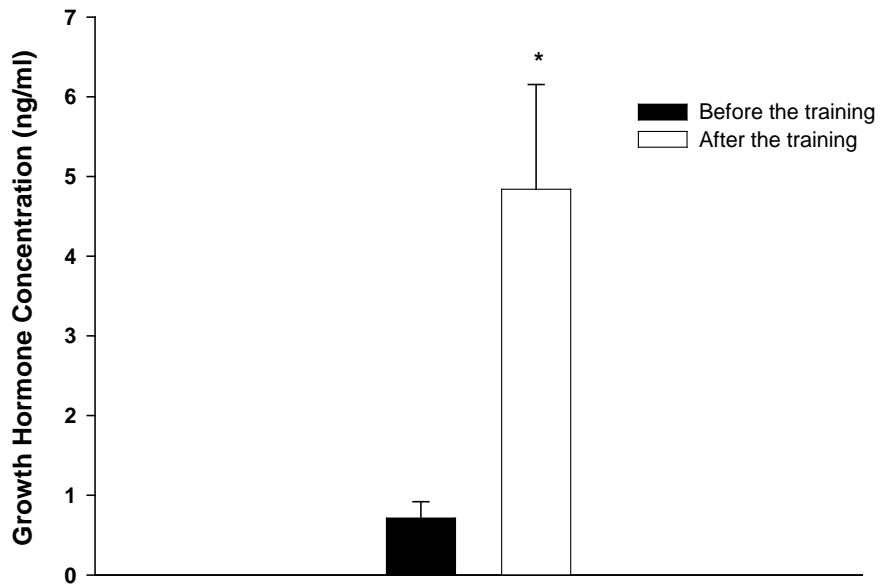
**Figure 2A**



**Figure 2B**

**Figure 2.** Isometric extension force (A) and isometric fleksion force (B) increased significantly after training period.(mean  $\pm$ SE)\*P<0.001

The GH concentration was the measured  $4.5 \pm 1.2$  ng/ml after the final training and this value is about five fold higher then pretraining GH level ( $0.86 \pm 0.20$  ng/ml). ( $p < 0.05$ ) (Figure 3).



**Figure 3.**Preexercise Growth Hormone concentration increased significantly after the final exercise in which blood samples were withdraw 20 minutes.\*p<0.05.

## DISCUSSION

In this study, we found that regular water training for two months increased lower extremity circumferential isometric muscle strength for knee extension and flexion and knee ROM. This finding agrees with previous literature regarding increased muscle development after regular exercise<sup>1,3</sup>. Growth hormone particularly plays an important role in the development of the musculoskeletal system and is known to increase depending on the type of exercise<sup>14,15,16</sup>. The increase in plasma growth hormone concentration after exercise leads us to conclude that swimming induced stress was enough to trigger the signal for musculoskeletal changes in our patients.

Although exercise is known to have an anabolic effect on muscle tissue<sup>17,19,20,21,22,23</sup>, our findings indicate that regularly performed simple physical activity models such as water exercise is efficient to elicit the desired response. Previous studies have shown an acute increase in growth hormone level with both aerobic and resistance training, while exercise is classically believed to stimulate release of growth hormone<sup>14,15,19</sup>. This hormone is of prime importance for musculoskeletal development and improvement of lean body mass<sup>14</sup>.

Significant improvement of post exercise knee ROM indicate that water exercise positively affects the the joint function. Similar improvement was observed for muscle circumflex and strength. These findings are in agreement with the literature describing increases in both the range of motion and muscle development after training<sup>1,3,11,19</sup>. The significant improvements in extremity circumferences and muscle strength observed after the trainings indicate that patients were affected by the water trainings.

The range of motion for knee joints in healthy people is 0° in full extension to 140° in full flexion<sup>29</sup>. A contracture is a limitation of joint movement and a deformity of the article often develops in

haemophilia patients<sup>18</sup>. Pretraining ROM evaluation had shown that our patients had a limited ROM with an average flexion angle for left knee 98.5° and right knee 96.6° due to previous attacks of hemarthrosis. Haris and Boggio showed that the knee flexion angle in adult haemophiliacs may decrease to less than 10°, demonstrating that nearly complete loss of knee function may develop with this disorder, which may progress further over the long term if precautions are not taken<sup>17</sup>.

Joint damage and atrophy of its supporting muscle tissue result with arthropaties due to anatomic structure changes as in hemophilic patients. Pain and limitation of ROM induced muscle spasm may negatively effect the kinematic characteristics of the extremity and quality of life<sup>11,17,26</sup>. Distention of muscle as in swimming may effect elastic quality characteristics of tissue surrounding the joint together with muscle-tendon complex and increase neuromuscular sensitivity<sup>11,12</sup>. Improvement of ROM that we observed in our study may be explained with repetitive movements that patients performed during swimming<sup>27,28</sup>. Considering the additional advantages of water exercises, including preventing spasms by relaxing muscles and decreasing pain, we propose that these exercises may be important for eliminating loss of function of the joint as well as for increasing muscle strength<sup>24</sup>.

Practicing water exercises against a certain amount of resistance is important for reversing muscle atrophy. Effective training program has to recruit the molecular signaling pathway for muscle development and continuity of exercise is essential for performance enhancement<sup>22</sup>. Thus any training modality for haemophilia patients with complications such as bleeding may reduce the quality of exercise. Therefore designing a safe exercise model with minimal trauma is crucial for those patients. Possible trauma and overused induced acute bleeding may cause interruption of training program. In our study, since no bleeding occurred during swimming program, we had been able to continue our training period without



interseption. Improved surface area with flippers may increase the physiological stress on leg muscles, that results enlargement of extremities circumflex and muscle strength.

Finally, all haemophiliac patients on prophylaxis replacement treatment may exercise should be started and continues training program may be a part of treatment strategies. In addition to the physical benefits of exercise it is also important to remember secondary gains of physical activity such as integration to social life and regaining self confidens. This study demonstrates that water exercise may be a valuable tool to induce muscle development and increase range of motion induced in haemophilia patients. Increased muscle strength and range of motion are very important for preventing disability and improving quality of life.

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