

# The Role of Physiotherapy and How Much it is Effective in Treatment of Joint Stiffness in Hemophilia Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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## Abstract

**Background:** Hemophilia is a group of hereditary diseases in which the body's ability to form blood clots and coagulate to prevent bleeding in the event of a ruptured vessel is impaired. Repeated bleeding over a long period eventually leads to chronic joint disease, which may manifest as arthritis, joint pain, or joint stiffness. This condition can lead to deterioration of quality of life and loss of organ function. **Objective:** This study, in the form of a systematic review, examines the role of physical therapy in affecting joint stiffness in hemophilia patients. **Materials and Methods:** PubMed, Embase, MEDLINE, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus databases were searched from inception to October 30, 2023. Mobility (timing and walking test) was included between the physiotherapy and control groups. **Results:** A total of 15 randomized controlled trial articles with 612 male hemophilia patients were included. In the comparison between the physiotherapy and control groups, the physiotherapy group experienced significantly reduced joint pain, increased joint range of motion, increased muscle strength, decreased Hemophilia Joint Health Score 2.1, and improved Six-Min Walk Test and Timed Up and Go Test performance or mobility. Comparisons show moderate- to high-quality evidence scores. **Conclusions:** Physiotherapy is effective in reducing pain, increasing joint range of motion, increasing joint health, and improving muscle strength and mobility in hemophilia patients.

**Keywords:** Hemophilia patients, physical therapy, stiffness of joint, systematic review

## INTRODUCTION

Deficiency of coagulation factors VIII (FVIII) or IX (FIX) causes hemophilia A or B, respectively. In this disease, recurrent bleeding occurs after trauma or spontaneously, depending on the coagulation activity of FVIII or FIX. If the plasma activity level is less than 1%, the disease is considered severe, between 1% and 5% moderate, and between 5% and 40% mild. Approximately 70% of patients are classified as having severe hemophilia.<sup>[1-24]</sup> People with severe hemophilia often suffer from bleeding into their joint cavities (hemarthrosis). Repeated bleeding over a long period eventually leads to chronic joint disease (arthropathy), which may manifest as arthritis, joint pain, or joint

stiffness. This condition can lead to deterioration of quality of life and loss of organ function.<sup>[2]</sup>

The first period of bleeding usually occurs between the first and third year, and the rate of disease progression depends on the number of hemarthroses.<sup>[3]</sup> Synovial tissue is a layer of cells that covers the inner surface of the

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joint capsule, and its function is to secrete and reabsorb synovial fluid. The function of synovial fluid or joint fluid is to lubricate cartilage surfaces to reduce friction and also to nourish cartilage cells.<sup>[4-7]</sup> The synovial tissue is full of blood vessels. One of the reasons why joints are one of the common places for bleeding in hemophilia patients is the large number of blood vessels.<sup>[8]</sup>

When the joint bleeds, the cells of the synovial tissue absorb the blood and remove it from the joint. In this process, the iron in the red blood cells gets stuck in the cells of the synovial tissue and gradually accumulates inside these cells. This accumulation of iron causes inflammation and thickening and increases the blood vessels of this tissue, and with the increase of blood vessels in the synovial tissue, intra-articular bleeding occurs more often.<sup>[9,10]</sup> On the other hand, the inflamed synovial tissue secretes enzymes that dissolve and consume the cartilage. With every bleeding event in the joint and reabsorption of blood, new unwanted cells grow in the joint capsule, which reduces its flexibility. As a result, the joint capsule gradually becomes small, compact, and inflexible, and then the joint becomes dry and limited in movement. Gradually, with the decrease in the range of motion in the joints, the limb muscles become weak, and after a while, with increasing destruction of the articular cartilage, the patient suffers from joint pain. Initially, the pain is only experienced during physical activities, but as the disease worsens, it may also be experienced while at rest. The bone density of the patient's limbs gradually decreases and they become porous.<sup>[10]</sup> All hemophilia patients who experience frequent joint bleeding have the aforementioned problems more or less in their knee, ankle, or elbow joints. With the increase in the patient's age and frequency of bleeding, the mentioned problems become more severe. At the same time, hemophilia patients who undergo appropriate replacement therapy and the use of blood factors for preventing joint bleeding will not have the aforementioned problems.<sup>[25]</sup> Hinge joints such as knees, ankles, and elbows are more prone to joint bleeding and complications, while the probability of these problems is less in ball and socket joints such as hip and shoulder joints.<sup>[11]</sup>

The multidisciplinary team aims to break this vicious cycle<sup>[12]</sup> using effective homeostatic treatment protocols and physical therapy, which includes resistance training, stretching, aerobic activities, and aquatic exercises.<sup>[12-16]</sup> The literature shows that even patients performing activities without joint involvement experience a decrease in physical performance, muscle strength, aerobic endurance, anaerobic endurance, and proprioception.<sup>[9]</sup> Hemophilia patients who prevent joint bleeding with appropriate replacement therapy and the use of blood factors will not have these joint problems. As mentioned, hinge joints such as knees, ankles, and elbows are more prone to joint bleeding and complications, while the probability of these problems is less in ball and socket joints, such as the hip

and shoulder joints. Concerning the methods of reducing joint complications in hemophilia patients, the importance of using physiotherapy treatments in these patients is such that physiotherapy in hemophilia patients leads to speeding up the process of repair of damaged tissues, reducing the number of bleeding episodes, preventing joint destruction due to frequent bleeding, and improving the quality of life of hemophilia patients.<sup>[17]</sup> Hemophilia patients need to restore joint and muscle movement after bleeding, and the physiotherapist helps them by reducing joint pain and stiffness, increasing muscle and soft tissue flexibility, and increasing the individual's balance. Physiotherapy for hemophiliacs includes electrotherapy, therapeutic exercise, and water. It is a treatment as well as electrotherapy that reduces inflammation and muscle spasms and reduces pain to prepare for joint mobilization.<sup>[19]</sup>

Therefore, the review of randomized clinical trial studies will lead to the systematization of different physiotherapy methods for pain reduction and better skeletal muscle performance of these patients. This systematic review aimed to analyze the effects of physiotherapy on joint stiffness in hemophilia patients.

## MATERIALS AND METHODS

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020.

### Search strategy

Systematic searches for randomized and non-randomized controlled trials were performed using the electronic databases PubMed, Embase, MEDLINE, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus based on search strategies recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. In addition, a manual search of the references of the presented articles was performed. This search was conducted in October 2023 using the following Medical Subject Heading descriptors: hemophilia, hemophilia, joints, physiotherapy, and physical therapy.

### Selection

The selection criteria of the studies are as follows.

- Clinical trials are randomized, non-randomized, and semi-randomized controlled.
- Include male hemophilia patients over 18 years of age.
- The intervention is alone or comparative.
- Clinical trials have examined at least one of each of muscle strength, muscle mass, range of motion, proprioception, joint pain, quality of life, dynamic and static balance, and walking and physical performance.
- Studies published in scientific journals are considered without limitation bias of publication year and language.

## Data extraction

Two independent researchers were employed to screen the data. In case of disagreement between the two researchers, a third researcher was consulted, and all three researchers reached a consensus by discussing and referring to the articles. In each article, the patient's condition, type of physiotherapy intervention, results, and duration of treatment and follow-up were included. In case of ambiguity in the required data of each study, the main researchers were contacted and given guidance.

## Data synthesis

Continuous data of outcome measures were recorded at the beginning and after the intervention. The longest available post-intervention time was considered post-intervention data for analysis. For calculating the mean and standard deviation for right and left joints for an outcome measure, the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions were used. In the control and intervention groups, the mean scores of the change in the Visual Analog Scale, joint range of motion, Hemophilia Joint Health Score (HJHS) 2.1, muscle strength, and Timed Up and Go (TUG) test were compared. Standardized mean difference (SMD) at 95% confidence interval (CI) was considered, and SMD values were approximately 0.2, small effect size 0.50, medium effect size, and large effect size 0.80.

## Data analysis

Cochrane Collaboration's Review Manager version 5.4.1 (London, England) for Windows was used for data analysis. In case of significant heterogeneity ( $I^2 \geq 50\%$ ), random effects analysis was used. If  $I^2 < 50\%$ , fixed effects analysis was applied. Subgroup analysis was performed in case of high heterogeneity or equivocal results.  $P$  value  $< 0.05$  was considered statistically significant.

## Bias assessment and quality classification

The Cochrane Collaboration tool was used to check the quality of the research studies. This was done using RevMan software version 5.3 (London, England) (Nordic Cochrane Centre, Cochrane Collaboration) which measures the risk of bias.

## RESULT

### Search results

The search results are presented in Figure 1. Initially, 5314 studies were found in the database. Then duplicates were removed, and 2815 articles were retained. A total of 74 eligible articles were identified and evaluated. Seventeen studies were included in the qualitative composition. After transferring two studies with repeated results, the meta-analysis included 15 studies with 612 male patients with an average age of  $38.53 \pm 16.69$  years, of which 512 patients had hemophilia A and 100 patients had hemophilia B.

## Methodological quality and the risk of bias within studies

The risk of bias diagram is summarized in Figures 2 and 3. Out of 17 studies, 11 studies have a good method to reduce bias. These studies have a low risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Two reviewed studies<sup>[12,13]</sup> had a high risk of bias in a randomized design, and two studies were at risk of other biases.<sup>[19,20]</sup>

## Inferential and statistical results

Among the included studies, one study<sup>[12]</sup> did not have the mean and standard deviation of the results, so the principal investigator was contacted to provide us with these numbers, and then they were used in the analysis.

### Pain intensity

The results of the investigations showed that joint pain in the physiotherapy group was significantly lower than that in the control group (SMD =  $-0.91$ ; 95% CI,  $-1.15$  to  $-0.58$ ;  $P < 0.001$ ). In the subgroup analysis, the exercise group performed significantly better than the control group in terms of knee pain intensity (SMD =  $-0.95$ ; 95% CI,  $-1.80$  to  $-0.83$ ;  $P < 0.001$ ). The intensity of elbow pain after manual therapy was significantly less than that in the control group (SMD =  $-0.81$ ; 95% CI,  $-1.25$  to  $-0.51$ ;  $P < 0.001$ ).

### Range of motion

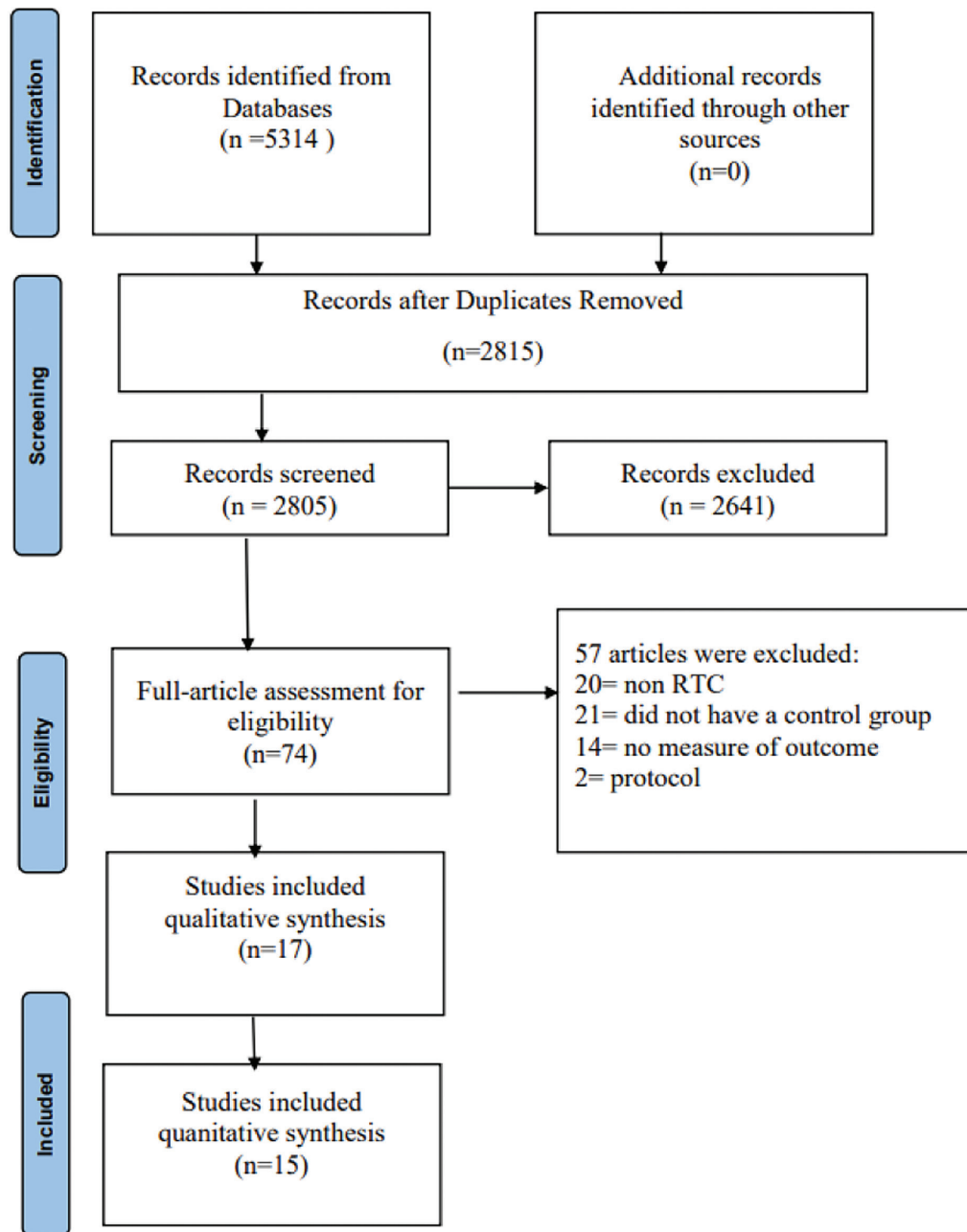
Investigations showed that the joint range of motion in the physiotherapy group was significantly higher than that in the control group (SMD =  $0.37$ ; 95% CI,  $0.19$ – $0.49$ ;  $P < 0.001$ ). In the subgroup analysis, the training group had a significantly greater range of motion for knee extension than the control group (SMD =  $0.41$ ; 95% CI,  $0.12$ – $0.71$ ;  $P = 0.02$ ), and the range of motion of the training group was significantly greater than that in the control group in terms of knee flexion (SMD =  $0.61$ ; 95% CI,  $0.32$ – $0.81$ ;  $P = 0.001$ ).

### Muscle strength

This study showed that muscle strength in the physiotherapy group increased significantly more than that in the control group (SMD =  $1.12$ ; 95% CI,  $1.15$ – $1.18$ ;  $P < 0.001$ ). In the subgroup analysis, muscle strength in the training group increased significantly for chest press (SMD =  $1.87$ ; 95% CI,  $0.91$  to  $2.23$ ;  $P < 0.001$ ), shoulder press (SMD =  $0.99$ ; 95% CI,  $0.43$  to  $1.56$ ;  $P < 0.001$ ), knee extension (SMD =  $2.37$ ; 95% CI,  $1.54$ – $2.94$ ;  $P < 0.001$ ), knee flexion (SMD =  $2.10$ ; 95% CI,  $0.57$ – $2.90$ ;  $P = 0.006$ ), calf raise (SMD =  $0.95$ ; 95% CI,  $0.72$  to  $1.42$ ;  $P < 0.001$ ), calf press (SMD =  $2.01$ ; 95% CI,  $1.01$ – $2.51$ ;  $P < 0.001$ ), and squat (SMD =  $0.99$ ; 95% CI,  $0.45$  to  $1.51$ ;  $P < 0.001$ ) than for the control group.

### Hemophilia Joint Health Score

The HJHS 2.1 of joints in the physiotherapy group was significantly lower than that in the control group (SMD =  $-1.14$ ; 95% CI,  $-1.26$  to  $-0.61$ ;  $P < 0.001$ ). In subgroup



**Figure 1:** The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram of the included studies.

analysis, elbow HJHS 2.1 (SMD =  $-0.92$ ; 95% CI,  $-1.23$  to  $-0.62$ ;  $P < 0.001$ ), knee HJHS 2.1 (SMD =  $-1.23$ ; 95% CI,  $-2.95$  to  $-0.51$ ;  $P < 0.001$ ), ankle HJHS 2.1 (SMD =  $-0.61$ ; 95% CI,  $-0.88$  to  $-0.12$ ;  $P = 0.001$ ), and total HJHS 2.1 (SMD =  $-2.95$ ; 95% CI,  $-4.01$  to  $-1.92$ ;  $P < 0.008$ ) were significantly lower than those in the control group. In the manual therapy group, the HJHS 2.1 score of elbows was significantly lower than that in the control group ((SMD =  $-0.67$ ; 95% CI,  $-0.91$  to  $-0.19$ ;  $P < 0.003$ ).

### Mobility (TUG performance)

Investigations showed that the improvement in TUG performance in the physiotherapy (exercise) group was

significantly higher than that in the control group (SMD =  $-1.33$ ; 95% CI,  $-1.97$  to  $-0.51$ ;  $P < 0.003$ ).

## DISCUSSION

This research comprehensively investigated the effects of physical therapy, including exercise, manual therapy, and modality therapy, on joint stiffness (joint pain, joint range of motion, joint health, muscle strength, and mobility) in patients with hemophilia. The results of the research showed that physiotherapy has positive effects on all the investigated parameters in patients with hemophilia.

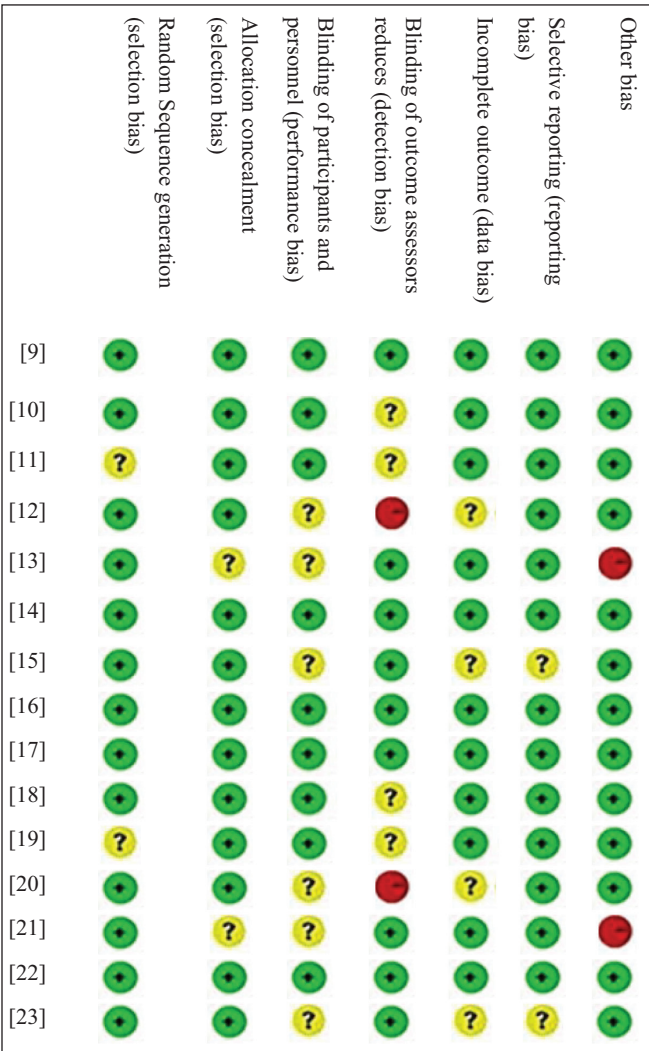


Figure 2: Risk of bias table

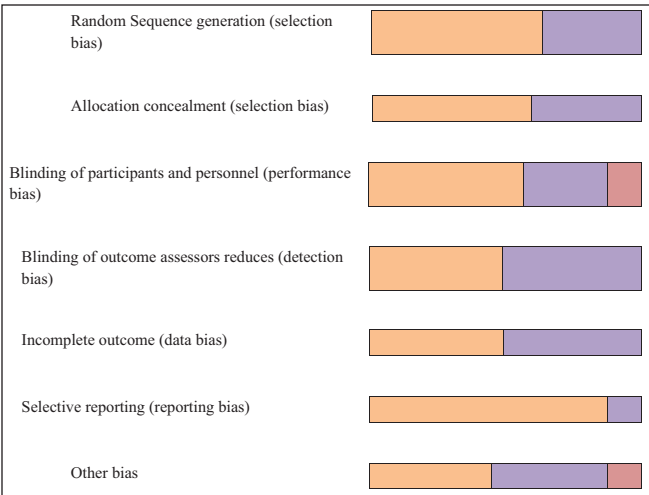


Figure 3: Risk of bias summary

This research shows that physiotherapy led to a reduction in pain in the intervention group compared to the control group. Researchers believe that exercise can reduce the

perception of pain because, during exercise, more blood circulation occurs in the joints, oxygenation increases, and pain decreases.

The effect of physiotherapy on the range of motion was significant but not highly significant. One of the reasons could be that the greater severity of hemophilia in patients may be associated with severe joint limitations or contractures. Therefore, the effect of physiotherapy to increase the range of motion can be limited.<sup>[26]</sup>

Also, the results indicated the effect of physiotherapy on muscle strength and TUG performance.

HJHS 2.1 is used to assess hemophilia patients. This may be because significant stress is created to increase muscle activity. In other words, it can be concluded that the vibrations transmitted to the muscles can lead to more stress on the muscles for voluntary control and maintenance.

### CONCLUSIONS

Physiotherapy can reduce joint pain, increase the joint range of motion, improve joint health, and improve muscle strength and mobility in patients with hemophilia. In this study, exercise was the most common type of physiotherapy. Exercise can be effective in reducing knee pain, making it easier to bend the knee and develop a range of motion; increasing the health of the elbow, knee, and ankle joints; and improving motor performance and muscle strength in chest press, shoulder press, knee extension, knee flexion, leg raise, leg press, and squat. Manual therapy may be effective in reducing elbow pain and improving elbow joint health.

### Conflicts of interest

There are no conflicts of interest.

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