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Original Article

Impact of Low-Dose Alendronate Therapy on Target Joints in Hemophilia Patients in a Low-Income Country

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Abstract

Background: Osteoporosis poses a significant clinical challenge for patients with hemophilia (PWH), primarily due to repeated intra-articular bleeding and joint inflammation. The objective of this study was to assess the impact of a combination of calcium-vitamin D and alendronate tablets on reducing the frequency of hemarthrosis in PWH in Lorestan province.

Methods: This non-randomized controlled trial involved a total of 118 PWH, out of which 55 patients with severe hemophilia A and B. Each patient underwent two assessments including the frequency and duration of bleeding episodes, and improvement in chronic joint pain, before and after receiving a combination of calcium-vitamin D, alendronate, tranexamic acid, and capsaicin ointment. Variables were measured at six-month intervals (at the beginning and end of the study). The statistical software used was SPSS version 21.

Results: The average age of the patients was 33.99 ± 10.67 years. The average number of target joints was 4.18 ± 0.88. A significant correlation was observed between the number of bleeding episodes before and after medication intake ($p < 0.0001$). Similarly, a correlation was found between pre- and post-medication atrophy around the target joint in PWH ($p < 0.0001$). However, no association was detected between joint ankylosis before and after drug administration ($p = 0.5$). Importantly, there was an improvement in chronic pain post-medication ($p < 0.0001$).

Conclusion: The findings suggest that the combination of calcium-vitamin D and low-dose intermittent alendronate can improve hemophilia joint condition.

1. INTRODUCTION

Hemophilia is an inherited X-linked disorder that results from a deficiency in three coagulation factors VIII, IX, and XI, called hemophilia A, B, and C, respectively. Hemophilia A (HA) and B (HB) are the most severe inherited bleeding disorders. Osteoporosis is an important clinical problem in patients with severe hemophilia and results in the lack of adequate motor activity, frequent joint bleeding, and joint inflammation. Low levels of vitamin D (VITD) in these patients are exacerbated by osteoporosis due to inactivity

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and reduced exposure to sunlight (1). Theoretically, VITD deficiency (especially in cold seasons) seems to be the cause of osteopenia and osteoporosis in patients with hemophilia (PWH) (2). Osteoporosis and complete VITD deficiency lead to increased pressure on the joints and recurrence of joint bleeding which eventually leads to permanent disability in these patients and landslides (defective and recurrent cycle of osteoporosis, hemarthrosis, joint pain, and immobility, decreased bone density, and osteoporosis). Due to these problems, patients with hemophilia develop premature and age-related osteoporosis. Therefore, significant disability, small and large bone fractures, and mobility limitations in these patients are inevitable (3). Primary prophylaxis with constant factor injection (between 2 and 18 years of age) is one of the strategies to delay arthropathy in these patients. However, there are different obstacles to the use of this treatment approach:

1- The formation of an inhibitor against FVIII or IX causes an increase in the number and severity of hemarthrosis and therefore, more severe synovitis (4).

2- Limited access to sufficient coagulation FVIII or IX for prophylactic treatment and even alternative therapy for periods of bleeding (5).

Given these barriers, efforts to use other alternatives to prevent bleeding and also interrupt repetitive bleeding cycles and intra-articular hypertrophic synovitis, have been ongoing for the past half-century. Two effective factors in preventing osteoporosis and osteopenia are bisphosphonate and vitamin D supplements. However, the role of prophylaxis of vitamin D, bisphosphonates, and pain relievers on the quality of joint bleeding in PWH is unclear and controversial. In this study, we used clinical criteria of joint destruction in rheumatoid arthritis (RA) arthropathy, which is similar to hemophilia arthropathy. The present study aims to assess long-term articular damage and function in PWH about the type of treatment based on RA damage indexes.

2. MATERIALS AND METHODS

2.1. Study population

This controlled clinical trial study was conducted on 55 PWH A and B. All patients are affected by severe hemophilia (FVIII or IX level below 1%). Patient attributes such as hemophilia type (A or B), disease severity (mild [factor 0.06 IU/mL-0.40 IU/mL], moderate [factor 0.01 IU/mL- 0.05 IU/mL] or severe [factor <0.01 IU/mL]), treatment plans (prophylaxis yes/no and initiation of prophylaxis before age 3 yes/no), inhibitor status, and Hemophilia Joint Health Score (HJHS) were documented. Written consent was obtained from all patients, and the study was approved by the Medical Research Ethical Committee (MREC) of Shahid Madani Hospital.

2.2. The inclusion and exclusion criteria

The inclusion criteria are FVIII or IX level below 1%, age over 15 years old, and the absence of complete disability.

The exclusion criteria are:

1. The occurrence of pathological fractures during or before taking the drug.
2. Development of muscular tetanus and Carpopedal spasm following the use of Alendronate.
3- Development of side effects such as nausea, vomiting, tinnitus, high blood pressure, and kidney stones while taking a combination of calcium and vitamin D.
4. Indications of metabolic bone disorder, a decreased level of serum 25-hydroxyvitamin D (<10 ng [25 nmol] per liter), simultaneous administration of medications that impact bone metabolism (such as bisphosphonates, calcitonin, or fluoride), impaired kidney function (creatinine clearance rate, <35 ml per minute), significant cardiac ailment, and a past occurrence (within the last year) of major upper gastrointestinal disease.

2.3. New assessment tools for hemophilia patients based on questioners

Patients' functional capacity was determined by using a variety of tools including the Health Assessment Questionnaire (HAQ), Modified Health Assessment Questionnaire (MHAQ), SF-36, and Arthritis Impact Scale (AIMS). Radiologic evaluation of hemophilic arthropathy was done using the Pettersson score. Joint damage in hemophilia patients was measured using the Rheumatoid Arthritis Articular Damage (RAAD) score. Pain levels and progression were tracked using the Visual Analogue Pain Scale (VAS) (FACES Scale) to compare pain severity among patients with similar conditions.

All patients had relatively regular visits to the hemophilia clinic before and after the intervention. The calcium-vitamin D combination, alendronate tablets, tranexamic acid capsules, and capsaicin factor cream are prescribed as follows:

1- Alendronate 20 mg once weekly for 6 months (low dose intermittent dose)
2- Calcium tablets: one a day in between
3- Pearl Vitamin D 50,000 units once a month
4- Capsaicin cream twice a day for 6 months
5- Tranexamic acid 500 mg QID 3 times a week (every other day).

Bone densitometry was not prescribed for all patients before and after intervention. Furthermore, the frequency of

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bleeding, reduction of chronic arthritis pain, joint ankylosis, number of bleeding days, atrophy of the joint, the interval between coagulation factor injection, and new bleedings were documented at six-month intervals (beginning and end of the study)

Patient information and physical examination before and after prescribing the drug were recorded in checklists. Possible side effects of medications (for alendronate: severe esophageal reflux, constipation, and changes in blood pressure and Capsaicin cream: skin reaction) were monitored monthly. Variables such as the number of joint bleeding per month and joint pain, pre-joint atrophy (with fabric meters and measurements) in quadriceps (hip), joint ankylosis (with moving angle and angle between thighs and legs), and joint encryption before and after Drug use was evaluated and recorded.

2.4. Statistical analysis

All data analyses were conducted using IBM SPSS version 23.0. Qualitative variables were displayed as frequency percentages, while parametric variables were presented as mean with standard deviation, minimum, and maximum values. The comparison between pre-and post-treatment results was assessed using paired t-tests, with statistical significance set at a p-value of less than 0.05. For data that did not follow a normal distribution, the Kruskal-Wallis test was used for analyzing differences among more than two populations.

3. RESULTS

The investigation included 55 patients diagnosed with severe hemophilia. The mean age ± standard deviation was 35.8± 12.9 years. The mean age± SD of onset of hemophilia arthropathy from birth was 7.2± 2 years. Approximately 3.6% of the patients had inhibitors against coagulation factors VIII and IX. A summary of the descriptive characteristics of the patients can be found in **Table 1**.

According to RAAD Score, the joint space narrowing in the elbow, knee, and ankle, as well as clinical indicators such as tenderness and joint swelling were significantly improved (p=0.001) (**Table 2**). VAS was significantly changed with the intervention (p=0.02). Furthermore, a significant difference in MHAQ score was found after intervention (p=0.01). The severity of atrophy around the joint did not significantly differ (p>0.05). Early joint indicators included tender joint Count and swollen Joint Count had improved after therapeutic intervention (p=0.001).

Table 1. The characteristics of the patients with Hemophilia A and B.

Parameters	Median (IQR)*
Age (y)	26.2 (21.7; 33.4)
BMI (kg/m2)	24.5 (21.3; 28.4)
Hemophilia A	39 (70.9)
Severe hemophilia	55 (100)
Prophylaxis statue	
No prophylaxis	47 (27.4)
Continuous prophylaxis	8 (14.5)
Frequency of prophylaxis per week	1.0 (1.3; 2.0)
frequency of prophylaxis	1 one time per week
HCV-positive	4 (6.4)
HIV-positive	0 (0)
History of joint surgery	5 (8.7)

*IQR: Interquartile range

Table 2. Comparison of RAAD, VAS, and MHAQ scores before and after the treatment.

Parameter	Before Int. Mean±SD (range)	After Int. Mean±SD (range)	P-value
RAAD score	**7.81±6.1 (0–45)**	**8.27±7.9 (0–43)**	**0.001**
VAS	3.19±1.7 (0–7)	3.85±1.5 (0–7)	**0.001**
MHAQ	**0.5±0.4 (0–2.5)**	**0.5±0.3 (0–1.5)**	**0.001**

RAAD: Rheumatoid Arthritis Articular Damage, **VAS:** visual analog scale (pain), **MHAQ:** Modified Health Assessment Questionnaire. Bold value is significant at p<0.05.

The correlation between the RAAD score and other independent variables wasn't significant (p=0.41). The median Pettersson score at the joint level (PS_{joint}) of affected joints was 6 (with a range of 3–9), and the median Pettersson score before and after the intervention was 14 and 11, respectively, which showed improvement (p=0.01).

With the statistical application of SF-36 and its negative number, both quality of life dimension and general health scale dimension (p<0.04) were related to emotional role (p<0.005). Age (> 40) with lower quality of life in four out of eight criteria (including physical function (p<0.023), physical pain (p<0.048), general health scale (p<0.029) and emotional (p>0.015) was related to lower quality of life. The relationship between adjusted and unadjusted HAQ scores and MHAQ scores was found to be 0.85 and 0.88, respectively. Notably, patients with more severe disabilities exhibited a significant disparity in their HAQ and MHAQ scores, particularly when comparing the MHAQ score to the final adjusted HAQ score. The inclusion of HAQ adjustment resulted in an average increase of 0.149 in the final score, and both adjusted and unadjusted HAQ scores were significantly higher (with means

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of 0.45 and 0.30, respectively) compared to MHAQ scores. The mean HJHS was higher in cases diagnosed after the age of 30 years as compared to cases that were diagnosed earlier (p=0.049) (**Table 3**).

Table 3. Correlation of HJHS with age of diagnosis

Age of diagnosis	Patients (n)	HJHS mean ± SD	p-value
< 30 years	16	4.96±8.37	0.049
≥ 30 years	39	5.68±11.5	
Total	55	5.06±9.98	

The mean PSjoint among the affected joints was 6, with an interquartile range of 3-9. Utilizing the consensus atlas, the PSjoint inter-observer confidence interval saw a notable rise from 0.94 (95% CI 0.91-0.96) to 0.97 (CI 0.96-0.98), indicating enhancement. Joint PS improved significantly after the intervention compared to before the intervention. Therefore, the real difference in the arthropathy of the patients was related to the difference in joint PS of more than 2 points before and after the intervention. A total of 57% of the enumerated joints experienced arthropathy. The median PS for all affected joints was 6, with an interquartile range (IQR) of 3-9. Similarly, the median PS for all patients was 22, with an IQR of 9-31. To assess the impact of the atlas on the consistency and concordance of joint PS and patient PS in a control population with varying degrees of hemophilic arthropathy, an additional analysis was conducted on abnormal PS values (i.e., those with at least one joint abnormality and PS > 0). In this subgroup analysis, the intervention resulted in an increase and enhancement of PS. Joint PS significantly improved from 0.88 (CI 0.81-0.92) before the consensus atlas to 0.94 (CI 0.91-0.96) with intervention and for PS patients from 0.92 (CI 0.80-0.97) to 0.99 (CI 0.97-0.97). After the intervention, the level of agreement increased from ±2.1 to ±1.5 points for PSjoint to ±6.9 to ±3.4 for PS patients. Values and percentages and medians Pettersson score in PWHs have been summarized in **Table 4**.

4. DISCUSSION

HA and HHB are recessive X-linked diseases characterized by acute bleeding in joints, muscles, and other organs, which eventually leads to hemophilic arthropathy and progressive disability. In addition to its direct destructive effect on the synovium, cartilage, and bone of the joint, intra-articular bleeding also causes a varusio chemical impact. Over time, blood is deposited in the form of hemosiderin deposits in these affected areas. Frequent and rapid repair of synovium causes hypertrophic synovium with loose vessels. Frequent bleeding of these joints in growing children causes wear of joint bone and progress of arthropathy. About 50% of patients with hemophilia suffer from permanent bleeding joint deformities (6).

Hemophilic arthropathy is a debilitating disease characterized by progressive joint destruction, chronic pain, and progressive reduction in quality of life. Recent evidence suggests that intra-articular inflammation and neoangiogenesis may be the main processes in the pathogenesis of hemophilia arthropathy (7). In a study conducted by Khaji M et al. in 2010, a total of 38 patients diagnosed with severe hemophilia were examined. The findings of the study revealed a noteworthy correlation between the duration and intensity of rigorous physical activity and bone density specifically in the L1-L4 lumbar spine. However, no significant relationship was observed between other aspects of physical activity and bone density in other areas of the body. It was observed that adult patients with hemophilia, who received long-term preventive measures and adequate factor injection, were able to sustain their bone density. Interestingly, the level of physical activity, in terms of both intensity and duration, played a minor role in the healing process of the joints in these patients (8). In 2009, Khaji M et al. showed in a study that there is no relationship between BMD and the severity of hemophilia. Results suggest that initiation of factor prophylaxis from childhood may maintain normal BMD in severe hemophilia (9). Based on a Swedish study in 2010, it was shown that with long-term prevention using sufficient factors, patients with hemophilia (PWH) maintain bone density, while the level of physical activity in terms of intensity and duration has little role in this process. has it. Also, these results may imply that the response to increased or decreased mechanical stress may be more important in maintaining bone density in sick children compared to adults. This also supports the importance of starting factor prophylaxis in the first years of life so that children can "When they reach puberty, they should have a more active life and normal bone density." (10). Continuous bleeding, deposition of iron pigment, and frequent bleeding causes true erosive and progressive arthritis. After frequent bleeding and chronic inflammation, the synovium thickens and causes the fragile hypertrophic tissue of the articular cartilage to undergo regression and wear, and subsequently forms subchondral bone, periosteal reaction, secondary osteophytes, and capsular fibrosis. The movements of the involved joint become more limited and eventually ankylosis and muscle atrophy occur in the joint and muscles around the joint (11).

Regular exercise is an essential part of effective treatment for improving motor function and reducing the risk of falls, osteoporosis, and pathologic fractures caused by osteoporosis.

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Table 4. Values and percentages and medians Pettersson score in PWHs.

	Series without consensus atlas (55 patients, 330 joints)	Series with consensus atlas (55 patients, 330 joints)	*p*-value
Joints with surgery	2.7 %	4.3 %	1.00
Pettersson score at the joint level			
Percentage abnormal scores	54 %	59 %	0.27
Median of all scores	6 (0–7)	0 (0–4)	0.44
Median of abnormal scores only	7 (3–9)	5 (2–9)	0.68
Pettersson score at patient level			
Percentage abnormal scores	80 %	75 %	0.72
Median of all scores	35 (10–46)	8 (2–20)	0.27
Median of abnormal scores only	36 (19–47)	13 (7–25)	0.23

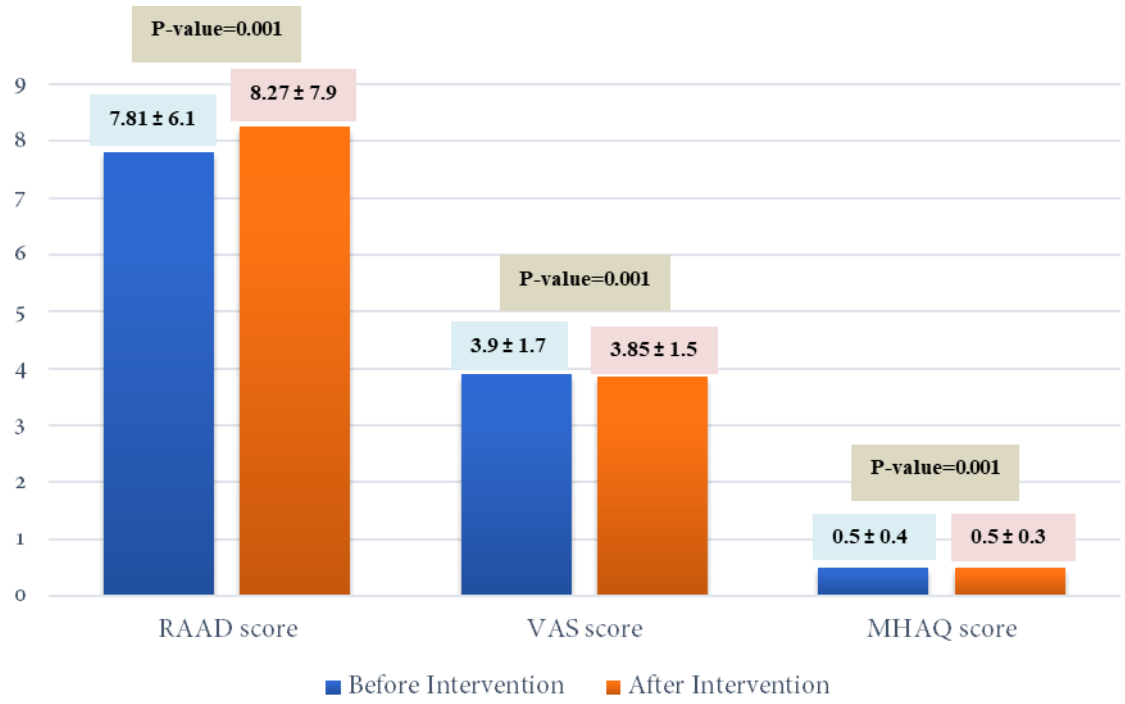

Figure 1. Comparison of clinical indexes before & after intervention. RAAD score: Rheumatoid Arthritis Articular Damage score; **VAS score:** Visual Analogue pain score; **MHAQ score:** Modified health assessment questionnaire score.

This exercise program should include aerobic exercise, balance strength training, and flexibility exercises. However, due to the specific challenges faced by individuals with hemophilia, such as a higher susceptibility to joint damage and easy bleeding, it is crucial for patients starting an exercise routine to seek evaluation from a trained physical therapist. This therapist should be affiliated with a hemophilia treatment center. Education and ongoing support are vital for maintaining joint health in hemophilic patients. Additionally, there are various aids available that can assist in making exercise more manageable and comfortable.

All studies show the role of alternative prophylaxis in the prevention of arthropathy, but in these studies, we did not find any evidence for the role of bisphosphonates in the prevention of arthropathy in hemophilia patients (12,13).

The joints of hemophilic patients are prone to early arthrosis in pre-middle age. Treatment with bisphosphonates has been effective in reducing pain, and stiffness and accelerating functional recovery in non-hemophilic OA patients (14), but in our study, hemarthrosis

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time, bleeding time, peri-articular atrophy, joint range of motion, and joint ankylosis had better results after the intervention.

Severe hemophilia causes a decrease in bone density (BMD). Patients at risk of bone density reduction are a group of hemophilia patients who have proven symptoms of hemophilia arthropathy. Because osteoporosis may complicate and challenge the future treatment of hemophiliacs, screening of patients with hemophilic arthropathy for decreased BMD and preventive treatment is highly recommended (15,16).

Adequate bone mineralization in childhood is recommended to prevent osteoporosis in older age along with bone density evaluation for adolescents with severe hemophilia, especially young and elderly patients with objective changes of hemophilia arthropathy. Management of osteopenic bone among patients with hemophilic arthropathy is necessary (17,18).

Prevention and diagnosis of osteoporosis in young PWH patients are very important. Prevention should promote good habits (such as a proper diet with calcium and vitamin D and exercise) and prevent harmful habits (such as tobacco, alcohol immobility, or high-impact sports). Prevention by frequent injection of factors and physical therapy treatments have made it possible to reduce the incidence and improve osteoporosis in people with hemophilia. Rehabilitation and exercise play a vital role in helping to prevent osteoporosis in young hemophilia patients. Osteoporosis should be treated regardless of the underlying cause (19).

Chronic pain is a common problem in hemophilia patients with arthropathy in developed countries, and vitamin D levels are often lower in people with chronic pain than in people without pain. Vitamin D supplementation has been investigated as a potential stand-alone treatment for chronic pain. In studies, there are recommendations for the use of vitamin D in the clinical practice of hemophilia patients with chronic pain (20).

This index (MHAQ scores) has never been used for PWH and has been used in chronic arthritis in RA patients (21).

This is one of the scoring systems used to evaluate the functional status of rheumatoid arthritis (RA) patients. The MHAQ and HAQ may be useful as measures of physical and motor ability in RA patients, but hemophiliac clinicians and researchers should choose the appropriate instrument for adjustment, and differences in scores between RA and hemophilia patients, especially at different levels. Find the disability.

This study shows that HAQ and MHAQ scores in patients with hemophilia (PWH) are good indicators for evaluating disability. Using HAQ or MHAQ alone or in PWH can be helpful. This could potentially be a powerful tool for physicians treating hemophilia in determining prognosis and determining physical disability. These markers alone may be more complete, and stronger than other clinical, laboratory, and radiographic features in evaluating disability. So far, no model has been proposed to convert MHAQ to HAQ for PWH. In individuals with chronic arthropathy, including those with hemophilia who fall into the least disabled category, the HAQ score shows a slight increase, approximately 0.5 units higher in the next category, and about 1.0 units higher in those with the highest level of disability. These variations hold clinical significance due to the notable differences between HAQ and MHAQ scores. Nearly two decades following the inception of HAQ, the Multidimensional Health Assessment Questionnaire (MD-HAQ) was introduced to specifically address pain, fatigue, overall health status, and morning stiffness in rheumatoid arthritis patients. Additionally, ankylosis and limitations in joint range of motion (ROM) were incorporated into this updated questionnaire. Perhaps medical strategies for improving physical performance in PWH by including work-related PWH conditions may leave these questionnaires appropriate for assessing hemophilia patients. Better access to physiotherapy and primary prophylaxis with factors VIII and IX in PWH under 15 years of age and better patient education over recent decades may have led to lower disability scores measured by HAQ, so without these disabilities, patients may be overestimated. The difference between adjusted and unadjusted HAQ scores in this study was not significant compared to the difference between the unadjusted HAQ the score is only slightly higher, it is about 0.5 units higher in the second quarter and about 1.0 units higher in patients with the highest disability. This difference in values is clinically significant because the HAQ and MHAQ scores are significantly different in the 2 groups. A Multidimensional Health Assessment Questionnaire (MD-HAQ) is used to evaluate pain, fatigue, general condition, and morning joint stiffness in RA patients. Almost 20 years after the introduction of the HAQ, ankylosis and decreased joint range of motion (ROM), both present in patients with RA, were added to this new questionnaire. Perhaps medical strategies for evaluating physical performance in PWH by including PWH conditions related to physical activity make these questionnaires suitable for evaluating hemophilia patients such as RA patients. Better access to physical therapy and primary prevention with factors VIII and IX in PWH under 15 years of age and better patient education in recent decades may have resulted in lower disability scores as measured by the HAQ, so patients without these

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disabilities may be overestimated. become the difference between adjusted and unadjusted HAQ scores in this study was not significant compared to the difference between unadjusted HAQ scores.

In general, the HAQ and MHAQ questionnaires can be used in the annual outpatient assessment of PWH. The use of short questionnaires such as the MHAQ alone in hemophilia clinics may have a weaker evaluation power than a single use of the HAQ in patients with high physical disability. In patients with high disability, the MHAQ may underestimate the degree of disability. We found that, as in RA patients in PWH, physical function measured by AIMS2 and MHAQ had left-skewed distributions and was insensitive to mild amounts of disability. However, both questionnaires had similar responses when used in similar hemophilia patients with progressive and chronic arthropathy at mild to moderate levels as an index of joint health status. Another important point to consider is the inconsistent nature of the HAQ score classification. For example, a 0.5-unit improvement in the HAQ from a baseline of 2.0 does not correspond to an improvement of 0.5 from a baseline HAQ score of 1.0.

Both questionnaires should be used simultaneously to increase the accuracy of arthropathy assessment in PWH. For this reason, HAQ components have recently been studied and their relationship with clinical variables has changed.

The current results indicate that both the MHAQ and HAQ can serve as reliable measures for evaluating the physical function of individuals with PWH, comparable to their use in RA patients. Overall, there is a strong concordance in outcomes across various questionnaires within the HAQ family (HAQ, MHAQ, MDHAQ, HAQ-II). In surveys where physical disability is less prevalent, the MHAQ may be adequate as a preliminary screening tool. However, for more precise clinical assessments, particularly in hemophilia patients with no limitations in disability, additional questionnaires should be employed in conjunction with the MHAQ. However, HAQ alone shows a higher diagnostic ability in patients with chronic arthritis, which may not be fully established in hemophilia patients. In patients with higher disabilities, the HAQ questionnaire should be used along with several paraclinical tests, and the economic aspect should not be considered in such patients.

The present study was designed to compare joint injury in patients with hemophilia (PWH) in the proposed palliative treatment regimen including low-dose intermittent Alendronate and mineral supplementation. In this study, the clinical index of RAAD as well as the functional status of MHAQ in hemophiliac patients were evaluated. RAAD score is a fast and possible way to measure joint damage in large populations of RA patients, but in this study, we used this questionnaire for the first time in PWH because of similar joint damage in RA arthropathy and hemophilia. In this study, there was a significant difference between RAAD scores before and after palliative treatment (p = 0.01). It is not clear whether this is due to the shorter duration of hemophilia arthropathy than the effect of 6 months of palliative care because bone densitometry has not been performed. Younger patients had higher RAAD scores at the onset of arthropathy (p = 0.004) and longer duration of arthropathy (p = 0.001).

In previous studies, the age of the patient was not related to the amount of joint damage. Also, the duration of hemophilia arthropathy was defined by previous studies as an independent and important predictor of joint damage (22). Joint damage and disability in PWH are directly related to the duration of arthropathy and steadily worsens in the first 20 years of hemophilia and progresses toward disability. These joint changes are similar to RA patients (23). There is a strong and direct relationship between joint damage and the rate of disability in long-term arthropathy. In the current study, there was no significant difference in terms of age (p = 0.57), VAS score (p = 0.078), and MHAQ score (p = 0.59) before and after the palliative treatment used in the study, but in the X-ray score (001) There was this difference. / p = 0) and the two variables had a significant correlation. The lack of change in VAS and MHAQ may be due to the short duration of palliative treatment in our study because perhaps increasing the duration of palliative treatment affects the level of disability.

Thus, RAAD score in PWH, like arthropathy in patients with rheumatoid arthritis, is correlated with MHAQ. RAAD scores were significantly better in patients who received coagulation factor alone without palliative treatment and who had joint damage and erosive arthropathy compared with patients who received coagulation factor in palliative care. This may be due to the fact that the use of palliative treatment reduces the patient's pain during the occurrence of hemarthrosis and causes the patient to delay the injection of the coagulation factor and the pain is masked as an alarm sign.

X-ray scores similar to RAAD scores were worse in patients who injected only coagulation factors without palliative care. Accordingly, some joint injuries can be attributed to a lack of joint care and inadequate coagulation factor injection. Treatment of hemophilia arthropathy has changed significantly. Initial treatment with our palliative medication regimen may lead to earlier control of inflammation and injury progression. It seems that inducing

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early recovery may prevent chronic arthritis and allow treatment to be reduced to drug-free recovery.

Alendronate may not be effective in reducing pain, and swelling and improving performance in a short time, also may not improve RAAD scores or MHAQs. It was found that erosive arthropathy was not higher in patients with inhibitors, but radiological damage to the joints before and after palliative treatment was significantly different.

One of the limitations of the study is the smaller count of PWH, so a larger-scale longitudinal study with a more balanced gender ratio and accurate results of future drugs is advised. Finally, the duration of arthropathy was the most effective factor in joint injury. There were more clinical complaints of joint damage in PWH who did not follow the recommended medication regimen. The risk of overall joint injury in PWH, as well as the association between bisphosphonate treatment and joint injury, requires further investigation in the PWH to elucidate their exact role and mechanism. In this study, it was observed that the mean HJHS score was higher in conditions without palliative treatment compared to those receiving palliative treatment. HJHS scores increase with age. Disability without palliative care regimens also increases. A study by La-or Chailurkit found that an alternating dose of 20 mg per week of alendronate was effective in improving many of the physical characteristics of joints in osteoporotic individuals, saving costs, promoting good immunity, increasing vertebral BMD, and stabilizing bone density (24).

Thus, in our study, high HJHS and consequent PWH inability were higher in cases where joint care was delayed and in patients who received less joint care, as well as in cases who did not receive palliative care. The mean HJHS in this study was higher in patients over 30 years (5.68 vs. 4.69) and in older patients (> 30 years) who had a longer duration of long-term traumatic arthropathy with less care (5.68 vs. 4.69).

This difference was statistically significant (P = 0.049). In previous studies, differences in the clinical value of different items on the HJHS questionnaire and the ability to estimate the potential for true joint health were demonstrated when using the current sequential scoring system. This is important for improving the clinical management of joint health in PWH in low-income countries. HJHS can distinguish between pediatric and adults with hemophilia and different treatment regimens. Reducing the items "Term Inflation" and "Crepitation" led to the creation of a new HJHS short questionnaire that had the same ability to differentiate. Further steps are required to achieve a much shorter assessment of HJHS (25).

An optimal clinical method for a detailed evaluation of a subject is challenging among experts for various reasons. In the study of Abdolwahab, Clinical evaluation was performed using physical examination. In this study, the difference between the radiological score of the WFH orthopedic committee and the clinical score of patients with the Arnold Hilgartner criterion was not significant, but the difference Radiological score and MRI was significant (r = 0.6, p = 0.02) (26).

Clinical use of biomarkers such as CRP, D dimer, and Ferritin can be very useful in early detection of PWH joint damage, but if standardization is not done, they have little effect on predicting clinical performance. We believe that standardization of biomarkers by linking them to clinical criteria and radiological parameters increases their predictive value in hemophilia arthropathy (27).

5. CONCLUSION

The use of a combination of calcium and vitamin D and a weekly intermittent low dose of Alendronate is effective in improving the quality of hemophilia's joint function, especially in reducing the incidence of hemarthrosis. Clinical evaluation of PWH by clinical questioners such as VAS, MHAQ, and joint clinical condition based on RAAD score is a useful and cost-benefit tool in low-income countries.

Ethical statement

It is hereby informed that your thesis entitled "Investigation of the effect of calcium-vitamin D combination and alendronate tablets on reducing the frequency of bleeding in target joints in Lorestan hemophiliacs" has been revised in Lorestan University of Medical Sciences with the ethics identifier IR.LUMS.REC.1397.170. The online version of the revised resolution is available at the following address and is open to the public: http://ethics.research.ac.ir/IR.LUMS.REC.1397.170

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Conflict of interest

The authors declare no conflict of interest.

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