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The importance of physical activity in the treatment of hemophilia

Znaczenie aktywności fizycznej w leczeniu hemofilii

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Abstract

Hemophilia is a genetically determined bleeding disorder characterized by a tendency for spontaneous bleeding, mainly into the joints, which can lead to arthropathy and significantly reduce the quality of a patient's life. The objective of this paper is to review the published literature on the impact of physical activity on the course of the disease and its role in current therapeutic protocols. Online databases were used to search for literature. The retrieved articles were analyzed. The review mainly included literature published after 2016. In the past, physical exercise was not recommended for people with hemophilia, primarily due to concerns about joint bleeding and the development of hemophilic arthropathy. Currently, regular, moderate physical activity plays a crucial role in the management of hemophilia, helping to strengthen muscles and improve joint stability, which can reduce the risk of bleeding. This shift in perspective is largely due to the availability of effective therapeutic options, mainly involving the replacement clotting factors. However, entirely new hopes for a permanent cure and the maintenance of physical fitness are brought by modern gene therapy treatments. Physical activity is essential for maintaining the health and fitness of individuals with hemophilia, and most exercises are safe due to effective prophylactic treatment. In addition to the benefits for joint health, regular exercise also helps prevent many lifestyle-related diseases.

Keywords: hemophilia, physical activity, exercises, hemophilic arthropathy

Abstrakt

Hemofilia to genetycznie uwarunkowane zaburzenie krzepnięcia krwi, które objawia się skłonnością do spontanicznych krwawień, głównie dostawowych, co może prowadzić do artropatii i znacznego obniżenia jakości życia chorych. Celem pracy jest przegląd opublikowanego piśmiennictwa, dotyczącego wpływu aktywności fizycznej na przebieg

choroby oraz jej miejsca w aktualnych schematach terapeutycznych. Do wyszukiwania literatury wykorzystano internetowe bazy danych. Wyszukane artykuły poddano analizie. Do przeglądu użyto głównie literatury opublikowanej po 2016 roku. W przeszłości ćwiczenia fizyczne były niezalecane u osób chorych na hemofilię. Wynikało to głównie z obawy przed wystąpieniem krwawień dostawowych oraz rozwojem artropatii hemofilowej. Aktualnie regularna, umiarkowana aktywność fizyczna odgrywa kluczową rolę w przebiegu hemofilii, pomagając wzmocnić mięśnie i poprawić stabilność stawów, co może zmniejszyć ryzyko krwawień. Zmiana nastawienia wynika z możliwości korzystania ze skutecznych opcji terapeutycznych, które opierają się głównie na podawaniu zastępczych czynników krzepnięcia - jednak zupełnie nowe nadzieje na trwałe wyleczenie oraz utrzymanie sprawności fizycznej, niesie za sobą leczenie za pomocą nowoczesnej terapii genowej. Aktywność fizyczna jest kluczowa dla utrzymania zdrowia i kondycji osób z hemofilią, a większość ćwiczeń jest bezpiecznych dzięki skutecznemu leczeniu profilaktycznemu. Oprócz korzyści związanych ze zdrowiem stawów, regularne ćwiczenia pozwalają też uniknąć wielu chorób cywilizacyjnych.

Słowa kluczowe: hemofilia, aktywność fizyczna, ćwiczenia, artropatia hemofilowa

Introduction

Hemophilia is a monogenic ally inherited blood disorder associated with genetic abnormalities in coagulation factors VIII (hemophilia A, HA) or IX (hemophilia B, HB) [1,2]. This disorder primarily affects males, as it is inherited in a sex-linked recessive manner, specifically on the X chromosome [3]. It occurs at a frequency of approximately 24.6 per 100,000 male newborns, with hemophilia A accounting for about 80% of cases, and approximately 40% of those developing a severe form of the disease [4,5]. It often manifests through recurrent bleeding into joints and skeletal muscles, leading over time to chronic pain, joint deformities, reduced mobility, and consequently, physical disability and decreased quality of life [6,7]. In the past, patients with hemophilia were discouraged from participating in sports due to the increased risk of injuries and associated bleeding. However, recent studies have documented medical, physical, and psychosocial benefits of sports participation, including improved muscle strength, joint health, and increased levels of endogenous factor VIII and von

Willebrand factor (VWF) [7]. Current conventional treatment mainly involves the supplementation of replacement clotting factors from early childhood; however, the development of inhibitors, or allo-antibodies, significantly reduces therapy effectiveness [1,6]. Therefore, modern gene therapies have been developed to provide a functional cure, aiming for the sustained expression of the missing clotting factor [8].

Purpose of the study

The aim of this work is to review the published literature on the impact of physical activity on the course of the disease and its role in current therapeutic protocols.

Review methods

Literature searches were conducted using online databases such as PubMed and Google Scholar. Articles were searched using English and Polish keywords, such as “hemophilia”, “physical activity in hemophilia”, “hemophilia treatment”, “hemophilia arthropathy”. The identified articles were analyzed, and the review primarily used literature published after 2015.

State of knowledge

General characteristics of the disease and modern treatment methods

Primary hemostasis in hemophilia patients is normal, resulting in the formation of a platelet plug [9]. Coagulation factors VIII and IX play complementary roles - factor VIII is a cofactor for factor IX, and this complex leads to the activation of factor X. This action strengthens thrombin production, which converts fibrinogen into fibrin, playing a crucial role in clot formation [9,10]. Thus, the deficiency of these factors causes clots to break down easily, rendering hemostasis ineffective [9]. Hemophilia can be classified into three groups based on the levels of these clotting factors - levels <1% are diagnostic for severe hemophilia, 1-5% for moderate hemophilia, and 5-40% for mild hemophilia [2]. Depending on the factor levels, patients may experience prolonged bleeding after injuries or surgeries, spontaneous joint bleeds, muscle bleeds, internal organ bleeds, or intracranial bleeds [5,11]. Recurrent joint bleeds - hemarthrosis - can lead to arthropathy, characterized by chronic synovial inflammation, hypertrophy, cartilage destruction, and muscle atrophy around the joint. Such damaged joints become less stable and more prone to further injuries [11,12]. This can also result in chronic

pain [11]. All these issues contribute to significant psychological burden for hemophilia patients [13]. In a survey study conducted among Polish men with hemophilia, it was shown that their quality of life is reduced due to limited employment opportunities about 43% of respondents are on disability pensions (although about 35% engage in additional work besides the pension), and only about 11% are professionally employed [9]. Due to treatment with blood-derived products, hemophilia patients are more prone to viral infections - in Owsianowska's study, 75% of respondents were infected with hepatitis C, associated with additional treatment [9].

To date, the main goal of hemophilia treatment has been to prevent spontaneous bleeds and control active hemorrhages. Long-term primary prophylaxis (initiated before the second joint bleed) in patients with severe hemophilia involves regular intravenous injections of the missing clotting factor [3,14]. Regular prophylaxis started in early childhood can significantly prevent arthropathy [15]. Standard plasma-derived concentrates have a relatively short half-life - about 10-14 hours for factor VIII and about 18-22 hours for factor IX [14,16]. This required frequent injections - about 2-3 times a week. Therefore, since 2010, efforts have been made to use engineering to create recombinant factors with a more favorable half-life, allowing longer circulation times and reducing the number of necessary intravenous injections. The first such drugs were introduced in 2014 (efraloctocog alfa, eftrenonacog alfa)
[16,17]. These drugs reduced the annual number of infusions by 30% in hemophilia A and 60% in hemophilia B compared to standard products [15].

In some patients receiving replacement therapy, neutralizing antibodies against the given clotting factors, known as inhibitors, develop, reducing the therapy's effectiveness [3,14]. In such cases, bypassing agents like activated prothrombin complex concentrate (APCC) and activated recombinant factor VIII can be used, but they need to be administered very frequently to be effective, posing a significant burden on the patient [3]. Therefore, other effective drugs have been developed. One of them is emicizumab, a subcutaneously administered monoclonal antibody that binds activated factor IX to factor X, restoring factor VIII function [18,19]. Clinical trials of emicizumab prophylaxis have shown effective bleed control and good tolerance in people with hemophilia A with or without inhibitors [20]. Other subcutaneous drugs acting on anticoagulant pathways include concizumab and fitusiran [3,21].

Despite the advancements in hemophilia treatment described above, there are still gaps related to safety, effectiveness, and the frequency of drug administration [3]. Thus, gene therapy holds promise for a complete functional cure, as its application in this disease has recently been

extensively researched. This therapy involves a one-time therapeutic intervention intended to have a lifelong effect [16]. This can be achieved by delivering a suitably modified gene (transgene) to the recipient's cells, allowing the body to produce the missing clotting factors [3]. Transgene carriers are vectors - they are divided into viral and non-viral. Adeno, retro, and lentiviral vectors are most commonly used [22]. Currently, gene therapy for hemophilia is based on two drugs approved by EMA (European Medicines Agency) and FDA (Food and Drug Administration) - Hemgenix (etranacogene dezaparvovec) for hemophilia B and Roctavian (valoctocogene roxaparvovec) for hemophilia A [23,24,25]. The possibility of using gene therapy in hemophilia is a relatively young topic, with studies having been conducted for only a few years, so their full effects, efficiency, and side effects have not yet been exhaustively described. However, studies conducted so far confirm the effectiveness of gene therapy. Increased activity of the missing clotting factor has been noted, leading to reduced bleeding despite stopping or reducing prophylaxis with factor VIII [8,16]. Another promising aspect is the possibility of permanent cure after a single administration of the drug [10], freeing the patient from frequent hospital visits. Consequently, an improvement in quality of life has also been reported according to the quality-of-life questionnaire for adults with hemophilia (Haem-A-QoL) [8]. However, some issues remain unresolved, the most serious being liver function disorders [15,18]. In a study involving 57 participants, 24 of them (42%) had elevated ALT levels after dezaparvovec, mostly mild. Five participants had ALT (alanine transaminase) levels 2-3 times above the upper limit of normal, and two participants even higher. In 17 of the 24 participants, elevations were observed within the first four months after vector infusion, and in 11 of 17, they resolved within the first four months, while in 9 participants, levels never returned to normal [26]. This phenomenon was more common in phase 3 studies of gene therapy for hemophilia A (89%) compared to gene therapy for hemophilia B (17%) [4]. Elevated liver values could be effectively treated with temporary immunosuppressive therapy, such as glucocorticosteroids [4]. Safety issues related to integration with the host genome and potential carcinogenesis remain topics of debate, although they are assessed as low risk because, according to liver biopsy studies, the vector DNA is found in episomal forms and does not integrate with the genome [4,15,18]. Other drawbacks of the therapy include an observed decrease in factor expression levels approximately 3 years after administration [18], as well as the exclusion of patients with antibodies against AAV (adeno-associated virus), which occur in about half of hemophilia patients [21]. Also, the option of potential re-administration of the transgene seems impossible at the moment, as patients treated with gene therapy develop a long-term specific humoral response to the adenovirus capsid, preventing re-transfer of the gene

using the same vector [15]. After addressing these challenges related to gene therapy for hemophilia, it will likely become the preferred treatment method [16].

Physical activity in patients with hemophilia

The literature presents arguments both for and against various sports activities for individuals with hemophilia [27]. However, it is now widely accepted that physical activity (PA) is essential for maximizing health in people with hemophilia [28,29]. This includes strengthening muscles around joints, maintaining joint mobility and bone health, and improving physical function.

The benefits of physical activity for patients with hemophilia
● Strenghtening muscles around joints
● Maintaining joint mobility
● Improving bone health
● Increasing factor VIII levels
● Reducing bleeding rates
● Preventing chronic secondary diseases (obesity, diabetes etc)

Table 1. The benefits of physical activity for patients with hemophilia

The World Federation of Hemophilia (WFH) encourages regular physical activity, noting that combining factor prophylaxis with exercise can reduce annual bleeding rates, including joint bleeds, and improve Hemophilia Joint Health Scores (HJHS) and quality of life (QoL) [7]. In the past, the role of exercise in hemophilia patients was limited, especially in contact sports, due to the high risk of injury and subsequent bleeding [27,29]. The primary concern with physical activity is the risk of hemarthrosis, particularly in the knees and ankles. Recurrent hemarthrosis can lead to pathological changes, such as synovial lining enlargement, hemosiderin deposition, subchondral cyst formation, and cartilage degradation, resulting in hemophilic arthropathy. This condition is characterized by chronic pain and limited joint mobility, which can lead to gait disturbances and even disability [30,31]. These factors

contribute to increased kinesiophobia (fear of movement) in hemophilia patients [32]. A study published in 2024 indicated that most individuals with hemophilia, including all participants aged 12-17, lead a sedentary lifestyle [33]. Bleeding events (spontaneous or traumatic) were reported in 43.7% of participants and were more frequent among those with a sedentary lifestyle compared to physically active individuals. This suggests that the intensity of physical activity is not directly related to increased bleeding risk. In fact, low physical activity is associated with poorer joint health and a higher risk of hospitalization [33]. Conventional treatment is now effective in maintaining a minimum level of clotting factor activity, allowing regular participation in sports for those with hemophilia. Additional benefits of exercise include maintaining a healthy weight, which prevents joint overload. Exercise has also been shown to increase factor VIII levels. Elevated plasma lactate levels from anaerobic exercise may improve factor VIII clearance, thus enhancing patient clotting [34]. Non-contact sports like swimming, running, and walking should always be promoted. However, high-risk contact sports such as rugby, boxing, soccer, and basketball, or any sports with a high risk of injury, are generally not recommended [34].

Recommended sports	**Non-recommended sports**
● Swimming	● Weighlifting
● Walking	● Extreme sports (ex. bungee jumping)
● Yoga & pilates	● Basketball
● Golf	● Volleyball
● Running	● Contact sports (ex. rugby, boxing)

Table 2. Recommended and non-recommended sports

Nonetheless, with proper prophylaxis, including correct dosing and timing of clotting factor administration and monitoring its levels in the blood, participation in contact sports is possible for hemophilia patients [27]. Beyond joint health, physical activity has a general positive impact on health, preventing secondary chronic diseases such as diabetes, obesity, cardiovascular diseases, and some cancers [34,35]. Electronic devices for monitoring PA can help patients achieve daily activity goals [35]. Combining physical activity with VR games is a novel approach that has been shown to increase physical activity levels [31].

Conclusions

Hemophilia remains an incurable disease that significantly impacts the daily lives of patients. However, advances in therapy over the past few decades have greatly improved patients' quality of life. Physical activity is increasingly recognized as essential for individuals with hemophilia, despite past concerns about the risk of hemarthrosis and subsequent joint damage. Regular exercise strengthens muscles, maintains joint mobility, and improves overall physical function, contributing to better joint health and quality of life. While high-risk contact sports are generally discouraged due to the potential for injury, with appropriate prophylaxis and factor administration, many people with hemophilia can safely participate in various physical activities. Sedentary lifestyles, on the other hand, are associated with poorer joint health and increased bleeding events, highlighting the importance of promoting safe, non-contact sports like swimming and walking. Additionally, exercise offers broader health benefits, including weight management and the prevention of chronic diseases.

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Conflics of interests

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Author contributions

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