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**PHYSICAL ACTIVITY AS PREVENTION AND
COMPLEMENTARY THERAPY IN DIABETIC
NEUROPATHY, DIABETIC RETINOPATHY AND
AGE-RELATED MACULAR DEGENERATION
IN THE ELDERLY: A LITERATURE REVIEW**

**Aktywność fizyczna jako profilaktyka i terapia uzupełniająca
w neuropatii cukrzycowej, retinopatii cukrzycowej i zwyrodnieniu
plamki żółtej u osób starszych: przegląd literatury**

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A - Koncepcja i projekt badania, B - Gromadzenie i/lub zestawianie danych, C - Analiza i interpretacja danych, D - Napisanie artykułu, E - Krytyczne zrecenzowanie artykułu, F - Zatwierdzenie ostatecznej wersji artykułu

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Abstract (in Polish):

Wprowadzenie: W obliczu starzenia się społeczeństw Europy i Ameryki Północnej wzrasta częstość występowania neuropatii cukrzycowej, retinopatii cukrzycowej i zwyrodnienia plamki żółtej. Leczenie farmakologiczne tych jednostek jest często niewystarczające. Dodatkowe nefarmakologiczne formy terapii i profilaktyki mogłyby spowolnić ten niekorzystny trend zachorowalności i poprawić jakość życia

pacjentów. W niniejszym artykule przeprowadzimy analizę roli aktywności fizycznej jako istotnego wsparcia procesu leczenia oraz jako czynnika ochronnego, zmniejszającego ryzyko zachorowania.

Cel pracy: Celem artykułu jest przegląd obecnego stanu wiedzy na temat pozytywnego wpływu ćwiczeń fizycznych w prewencji i terapii neuropatii cukrzycowej, retinopatii cukrzycowej oraz zwyrodnienia plamki żółtej. Celem artykułu było również zwrócenie uwagi na to, jaki rodzaj aktywności fizycznej pozwoli na osiągnięcie najbardziej optymalnych efektów.

Materiały i metody: Artykuł przeglądowy został napisany w oparciu o internetowe bazy danych: PubMed, Google Scholar, Polska Bibliografia Lekarska, znajdując łącznie 23 rekordy, wybranych na podstawie „słów kluczowych” wypisanych poniżej. Autorzy starali się użyć najnowszych badań oraz metaanaliz, ograniczając lata publikacji do 2014-2023.

Wyniki: Ćwiczenia aerobowe zmniejszają częstość występowania i ryzyko progresji wymienionych chorób. Ponadto w przypadku neuropatii cukrzycowej ćwiczenia oporowe ukierunkowane na określone partie kończyn mogą również zmniejszyć objawy bólowe i ryzyko upadków.

Wnioski: Aktywność fizyczną jako profilaktykę i terapię uzupełniającą w neuropatii cukrzycowej, retinopatii cukrzycowej i zwyrodnieniu plamki żółtej u osób starszych należy rozpatrywać jako działania skuteczniejsze niż prowadzenie leczenia wymienionych chorób bez tej aktywności. W obliczu tych obserwacji, aktywność fizyczna powinna stać się elementem opieki długoterminowej oraz profilaktyki.

Abstract (in English):

Introduction: In the face of aging societies in Europe and North America, the incidence of diabetic neuropathy, diabetic retinopathy and macular degeneration is increasing. Pharmacological treatment of these entities is often insufficient. Additional non-pharmacological forms of therapy and prevention could slow down this unfavorable trend of morbidity and improve the quality of life of patients. In this article, we will consider physical activity as a support for the healing process and a protective factor.

Purpose of the work: The aim of the article is to review the current state of knowledge regarding the positive impact of physical exercise in the prevention and therapy of diabetic neuropathy, diabetic retinopathy and age-related macular degeneration. The goal was also to draw attention to what type of physical activity is best for achieving the most optimal effects.

Materials and Methods: The review article was written based on online databases: PubMed, Google Scholar, Polish Medical Bibliography. The authors tried to use the latest research and meta-analyses, limiting the years of publication to 2014-2023.

Results: Aerobic exercise reduces the incidence and risk of progression of the above-mentioned diseases. Additionally, in the case of diabetic neuropathy, resistance exercises targeting specific parts of the limbs may also reduce pain symptoms and the risk of falls.

Conclusions: Physical activity as prevention and complementary therapy in diabetic neuropathy, diabetic retinopathy and macular degeneration in the elderly should be considered more effective than treatment of the above-mentioned diseases without this activity.

Keywords (in Polish): aktywność fizyczna, neuropatia cukrzycowa, retinopatia cukrzycowa, zwyrodnienie plamki żółtej.

Keywords (in English): physical activity, age-related macular degeneration, diabetic retinopathy, diabetic neuropathy.

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Short title

Aktywność fizyczna jako terapia u osób starszych: przegląd

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P. Załęcki et al.

Introduction

Numerous studies in recent years have shed light on physical activity, which turns out to be an important factor affecting overall health [1]. In addition to overall improvement in the functioning and efficiency of the body, it is finding increasingly significant application in the prevention and treatment of many specific disorders, including neurological diseases. This group of diseases ranks third among the most common causes of disability and death in Europe, and considering the aging society, the trend of occurrences has been consistently increasing for many years [2]. The United States is also affected by this issue, which is progressively becoming more prevalent [3]. Older age not only affects the course and clinical picture of diseases but is also the main factor increasing the risk of neurological diseases [4]. Therefore, interventions are sought that could have a significant positive impact on the treatment and prevention of disorders affecting the nervous system.

Diabetic neuropathy, retinopathy, including diabetic retinopathy, and age-related macular degeneration are just a few of many diseases in which pharmacological treatment alone is often insufficient, and the risk of their occurrence increases with age [5, 6, 7]. For this reason, additional non-pharmacological forms of therapy and prevention could slow down this unfavorable trend of increased incidence. In the light of the latest research, the most promising of them is regular physical activity.

Materials and Methods

The review article was written based on online databases: PubMed, Google Scholar, Polish Medical Bibliography, finding a total of 23 records, selected on the basis of the „keywords” listed below. The authors tried to use the latest research and meta-analyses, limiting the years of publication to 2014-2023. The publications on which the article is based were found and analyzed by members of the Interdisciplinary Scientific Club of Geriatrics, associated with the Department of Geriatrics, Collegium Medicum, Nicolaus Copernicus University in Toruń, composed of: Piotr Załęcki, Monika Rudewicz, Bartosz Mazur, Aleksandra Mazur. The team was supervised by physician Jakub Husejko

from the above-mentioned Department. The data collection process was carried out using the Zotero tool.

Results

A total of 23 records were found in the online databases listed above, meeting the following inclusion criteria: they related to the topic of our scientific article, met the above-mentioned „keywords” and were published between 2014 and 2023.

1. The Impact of Physical Activity in Diabetic Neuropathy

1.1 Overview

In 2017, the number of diabetic patients was 451 million, and the forecasts for 2045 speak of as many as 693 million patients [8]. The World Health Organization consistently expresses concern regarding the alarming rate of increase in the number of patients. At least 50% of people with diabetes experience peripheral neuropathy [9]. The main risk factors for diabetic peripheral neuropathy include the duration of diabetes and the patient's age [5]. Increased HbA1c, low HDL concentration and overt proteinuria are also mentioned as risk factors [10]. There is a significant social and health burden associated with diabetes and its complications, such as peripheral neuropathy. Proper prevention, including not only blood glucose control, proper diet, or quitting smoking, but also regular physical activity, can play a key role in preventing and reducing the symptoms of diabetic neuropathy.

1.2 Physical activity reduces the symptoms of neuropathy more effectively than diabetic foot care alone.

A study was conducted on a group of 103 individuals aged 55 (± 10 years) suffering from Diabetic Peripheral Neuropathy (DPN). The study, lasting 8 weeks, compared a research group engaged in exercises such as wrist stretches, golf ball circling, thumb circling, tapping with the foot, ankle rotations, and tennis ball rolling, with a control group that received standard care and education regarding diabetic foot care. The results were assessed using the Patient Neurotoxicity Questionnaire, as well as evaluations of neuropathy severity and pain levels, along with physical tests measuring hand and foot functions. After 8 weeks of intervention, the exercise group demonstrated significantly greater improvement in motor scores and in performing daily activities such as stair climbing and household tasks, as well as a reduction in pain symptoms [11].

The usefulness of exercise as a support for lower limb care was confirmed by another study in which a group of 78 volunteers with diabetic neuropathy (DPN) was tested to evaluate the effectiveness of therapeutic foot and ankle exercises in improving daily physical activity and walking speed. Exercises were performed for 12 weeks, while the control group used only standard care of the lower limbs. The results of the study confirmed a significant improvement in walking speed, ankle range of motion, and vibration perception compared to the control group. The improvement in these aspects was maintained in the intervention group even one year after the end of the study [12]. Therefore, adequate physical activity reduces the symptoms of peripheral neuropathy more effectively than diabetic foot care alone.

1.3 Physical activity reduces the risk of falls

Individuals suffering from Diabetic Peripheral Neuropathy (DPN) are more susceptible to falls due to slower reactions, altered gait, and impaired postural control compared to those unaffected by this condition [13]. Regular participation in routine exercise may help improve health and reduce symptoms in these individuals [14]. Strength exercises might exhibit effectiveness in this regard. Following a 16-week cycle of intensive resistance exercises, including knee extensions, ankle presses, leg presses, and quasi-isometric exercises (rapid knee extension and rapid ankle dorsiflexion), patients subjected to the intervention achieved a significant increase in the speed of generating force in the ankle and knee joint. As a result, their stability when going up and down the stairs increased, and thus the risk of falls decreased [15].

A key aspect of maintaining stability, especially for individuals in advanced age, is proper proprioception, which refers to the ability to sense body position in space [16]. Performing general development exercises such as squats, standing on one leg, heel and toe lifts, and exercises on an unstable surface resulted in an improvement in proprioception and nerve conduction speed in people with diabetic neuropathy. These effects were observed after an eight-week training cycle, which took place three times a week [17].

1.4. Aerobic training improves the prognosis of diabetic peripheral neuropathy

In recent years, two studies have highlighted the particularly positive effects of aerobic exercise for patients with diabetic neuropathy. Both studies were conducted by the team of Gholami et al. In the first one, the experimental group took part in aerobic training, which consisted of 20-45 minutes of walking or running on a treadmill, at an intensity of 50-70% of their heart rate reserve. These exercises were performed three times a week for a duration of 12 weeks [18]. In the second study, individuals in the experimental group underwent training on a stationary bike ergometer lasting from 30 to 45 minutes, also at an intensity enabling them to achieve 50-70% of their heart rate reserve. This study also lasted for 12 weeks, with training taking place three times a week [19]. Compared to the control groups, the training subjects showed a significant increase in the sural sensory nerve conduction velocity (NCV) [18], a decrease in the concentration of HbA1c in the blood [18,19], an improvement in the MDNS score (a scale that assesses the severity of peripheral neuropathy) and an improvement in blood supply to the lower limb (increase in flow-mediated dilation (FMD) [19]. The results of these studies therefore suggest that aerobic exercise may slow the progression of diabetic peripheral neuropathy.

2. The influence of physical activity in retinopathy

2.1 Overview

The aging population of developed countries is increasingly faced with the problem of eye damage and emerging blindness [6,7]. In the face of the current and projected increase in this phenomenon, physical activity has been studied as a potential effective tool in the prevention and treatment of eye diseases. Physical activity, by positively influencing the functioning of the nervous system, also has a beneficial impact on the functioning of the eye. This is due to the shared embryological origin of the central nervous system and certain parts of the eye, including the retina [7]. Many literature reviews suggest that lower physical activity is associated with an increased risk

of certain eye diseases, such as macular degeneration, diabetic retinopathy, and glaucoma, among others. On the other hand, in people already affected by eye diseases, physical activity indicators are also reduced compared to people without these diseases [7, 20].

A study was conducted in which the study group consisted of elderly people participating in recreational activities. The respondents themselves reported the level of participation in six categories of activity. A clear decrease was observed in five out of six tested types of activity in people with visual impairments [7].

2.2 The Protective Impact of Physical Exercises on the Retina

Research shows that physical activity, apart from protecting the retina, also provides anti-inflammatory effects in this area of the body [21]. Diabetic retinopathy and macular degeneration (AMD) are eye diseases associated with vision loss in which the cells of the retina degenerate. Exercise has been shown to reduce the risk of AMD and further improve vision quality scores [21,22].

Considering that inflammation is an important factor involved in the pathogenesis and progression of these diseases, physical activity may be an important preventive and therapeutic factor in these conditions. The exact mechanism behind the beneficial effects of exercise on retinal health is unknown, but there is a potential role for myokines, with interleukin-6 (Il-6) being the main one. It has pro- and anti-inflammatory effects, which depends on the location. In the retina, its inflammation-promoting function is more pronounced. It has been noticed that patients with diabetic retinopathy have elevated levels of interleukin-6, VEGF and interleukin-8. On the other hand, during physical activity, interleukin-6 is released by skeletal muscles, which in this case exhibits anti-inflammatory effects, associated with its inhibitory influence on interleukin-1 β and tumor necrosis factor-alpha (TNF-alpha). Through this mechanism, physical activity provides the body with reduced susceptibility to chronic inflammatory conditions [21].

2.3 Macular degeneration

Macular degeneration is one of the most common causes of vision loss over the age of 50 in developed countries [7, 23]. The pathogenesis of this disease is not fully understood, and the possibilities of its prevention are significantly limited. However, it was noticed that dysregulation of the complement system and oxidative stress play a role in its development. Physical inactivity may contribute to the development of this condition by promoting the formation of macular drusen precursors. Additionally, low levels of physical activity promote inflammation and endothelial dysfunction, leading to AMD progression [7,24].

There are several studies that highlight the protective effect of physical activity on the progression of AMD. In addition, it has been shown that physical activity modifies the impact of vision loss on the overall quality of life in patients with bilateral macular degeneration [7].

Regular physical activity can be considered a protective factor in the case of macular degeneration. This is due to the increase in resistance to oxidative stress, which is a factor in the development of AMD, and the increase in the activity of antioxidant enzymes. This effect also plays a role in preventing the progression of macular degeneration. A higher level of physical activity in both men and women correlates with a lower risk of macular drusen. In addition, a higher BMI is

associated with a higher risk of advanced AMD, and physical activity as a way to reduce body weight will therefore be a method of reducing this risk. [25]

The Melbourne Collaborative Cohort Study presented a report based on participants' self-assessment of physical activity, which showed an inverse relationship between frequent, vigorous exercise and the incidence of moderately severe AMD in women. It also showed a lower risk of moderate to late-stage AMD with more frequent (3 or more times a week) and less frequent (1-2 times a week) intensive physical exercise [25].

Importantly, studies have also demonstrated a reduction in the risk of AMD progression to an advanced stage with higher levels of physical activity, and an active lifestyle can decrease the risk of developing macular degeneration by up to 70% over a 15-year period [7].

2.4 Diabetic retinopathy

A broadly understood lifestyle is a significantly modifying factor in the risk of developing diabetes and, consequently, its complications that affect multiple systems within the body, including the visual organ.

The very lack of physical activity, as an extremely important element of a healthy lifestyle, significantly contributes to the increase of this risk and may account for up to 27% of all its causes [21].

Speaking of the organ of vision, one of the most common complications of diabetes is diabetic retinopathy, which belongs to the group of microvascular complications and is one of the main causes of total vision loss [21, 26]. It is a complex disorder affecting mainly the retinal capillaries (microangiopathy) induced, among other factors, by hyperglycemia. The risk of its occurrence and progression increases with the duration of diabetes and the level of hyperglycemia. [27]

Physical activity is strongly correlated with the risk of diabetic retinopathy [21,28]. It has been observed that incorporating and/or increasing physical activity and reducing a sedentary lifestyle are associated with the prevention of the onset, progression, and severity of diabetic retinopathy. Despite the mechanisms being unknown, this relationship is noted to occur in both type 1 and type 2 diabetes. However, the specifics of the type and frequency of physical activity undertaken have yet to be specified [21].

Years of research have led to an expanded perspective on diabetic retinopathy, not only as a microvascular complication, but also emphasizing the connection between retinal microcirculation and neurons, as well as glial cells, where pathological changes due to diabetes occur more rapidly than in vessels. In addition, taking into account the complexity of the pathophysiology of diabetes, the role of inflammation, which is supposed to contribute to the development of diabetic retinopathy, is increasingly taken into account. In this context, the issue of the functional relationship between neurons and glial cells is approached with increased emphasis [29].

Firth and Loprinzi conducted a study involving individuals aged 40 to 85. The group comprised 157 individuals, in whom the relationship between strength training and moderate to vigorous physical activity with chronic inflammation was observed. By examining the concentration of C-reactive protein (CRP), it was noticed that such physical activity was inversely proportional to chronic inflammation. However, such a connection was not proven in the case of resistance training exercises targeting muscle strengthening [30].

Aerobic exercise contributes to the inhibition of oxidative stress and inflammation, and on the other hand, a sedentary lifestyle contributes to an increase in the incidence of retinal dysfunction in diabetic patients. Thus, aerobic exercise may be the main non-medical method of preventing DM complications [31].

Conclusions

The presented evidence suggests that regular physical activity has a positive impact on the mentioned medical conditions. Introducing and/or increasing physical activity, especially aerobic exercise, can serve as an effective preventive method in eye diseases and vision loss. Consequently, it encourages the incorporation of physical activity-related recommendations into daily medical practice, as it represents a cost-effective and non-invasive protective and therapeutic approach. In addition, an important issue arising from this topic is the solution to the problem of a sedentary lifestyle in people with visual impairment, in whom emphasis should be placed on physical activation in everyday life [7,28]. Similarly, in the case of diabetic neuropathy, aerobic physical activity may inhibit the progression of the disease by improving blood flow and sensory conduction of the limbs.

However, the term „regular physical activity” should be precisely defined to provide patients with accurate recommendations. Following the guidelines of the World Health Organization, individuals aged 65 and above are advised to engage in moderate-intensity aerobic physical activity for 150-300 minutes per week, or vigorous-intensity activity for 75-150 minutes per week, or an equivalent combination of these two intensity levels. By adhering to these guidelines, patients should achieve benefits similar to those mentioned in the cited studies. [32]

Despite more evidence for the positive effects of aerobic exercise, resistance exercise should not be abandoned. The results of the research suggest that regular physical activity, primarily as specific exercises that stimulate the muscles of the lower limbs, improves motor functions in patients with diabetic neuropathy. They can reduce pain symptoms and the risk of falls and improve the daily functioning of patients. Therefore, choosing an individual training plan combining both aerobic and anaerobic exercises will be the best recommendation for patients.

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