Clinical and Experimental Health Sciences

Review / *Derleme*

The Effects of Different Exercise Modalities in Alzheimer's Disease

Farklı Egzersiz Yöntemlerinin Alzheimer Hastalığındaki Etkileri

Dilek Özbeyli, Özgür Kasımay Çakır

Department of Physiology, Marmara University School of Medicine, İstanbul, Turkey

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common cause of dementia. Increased oxidative stress, abnormal amyloid β (Aβ) accumulation, tau aggregation, neuroinflammation, neuronal plasticity failure, and neuronal loss are the main factors related to the pathophysiology of AD. Increasing evidence suggests that physical activity has a positive effect on both cognitive function and cellular pathologies of AD. It has been demonstrated that aerobic exercise (AE) increases the activity of antioxidant enzymes and synthesis of neurotrophic factors, decreases the levels of neuroinflammatory markers, and enhances the functions of learning and memory. It is also beneficial for the improvement of cell survival and upregulation of Aβ clearance. AE has been shown to reduce the levels of soluble $A\beta_{1-42}$ via an increase in enzyme activity, which is responsible for the upregulation of Aβ clearance in brain tissues. It also represses apoptotic cascades such as the caspase-9, cytochrome c, Bax, and caspase-3 cascades. Although there are no clear data on the effects of resistance exercise (RE) on AD, only a small number of articles have studied the effects of RE on models of aging. In these studies, RE increased the serum concentrations of insulin-like growth factor-1 and brain-derived neurotrophic factor (BDNF), reduced oxidative stress in humans, and upregulated the hippocampal expression of BDNF mRNA in animals. In addition, RE and AE therapies may help progress in daily activities and enhance physical ability in AD patients. Eventually, exercise therapy regimens may lead to more effective treatment options and slow the progression of AD without any side effects.

Keywords: Alzheimer's disease, exercise therapy, antioxidant enzymes, neuronal plasticity

Öz

Alzheimer hastalığı (AH) ilerleyici nörodejeneratif bir hastalık olup demansın en sık görülen nedenidir. Artmış oksidatif stres, anormal amiloid β (Aβ) ve tau proteinlerinin birikimi, nöroinflamasyon, nöronal plastisite yetmezliği ve nöronal kayıp AH'nin patofizyolojisi ile ilişkilendirilen ana faktörlerdir. Artan kanıtlar fiziksel aktivitenin, hem kognitif fonksiyona hem de AH'de gözlenen hücresel patolojilere iyileştirici etkileri olduğunu göstermektedir. Aerobik egzersizin (AE) antioksidan enzim aktivitesini, nörotrofik faktörlerin sentezini arttırdığı, nöroinflamatuar belirteçleri azalttığı, öğrenmeyi ve bellek fonksiyonlarını iyileştirdiği gösterilmiştir. Ayrıca hücre yaşayabilirliği ve Aβ klirensi üzerine yararlıdır. AE, beyin dokusundaki çözülebilir $A\beta_{1-42}$ düzeylerini klirensten sorumlu enzimlerin aktivitelerini arttırarak düşürür. Aynı zamanda kaspaz-9, sitokrom c, Bax ve kaspaz-3 gibi apoptotik enzimleri baskılar. Direnç egzersizlerinin (DE) AH'deki etkileri hakkında açık bir bilgi bulunmamakla birlikte az sayıda çalışmada daha çok yaşlanma modellerinde etkilerine bakılmıştır. Bu çalışmalarda DE'nin insülin benzeri büyüme faktörü-I ve beyin kaynaklı nörotrofik faktörün (BDNF) serum konsantrasyonlarını artırdığı, oksidatif stresi azalttığı insanlarda gösterilmiş olup, hayvanlarda hipokampal BDNF mRNA düzeyinde artış yaptığı bildirilmiştir. Ek olarak DE ve AE, Alzheimer hastalarında günlük aktivitelerin gelişimine ve fiziksel becerilerin arttırılmasına yardımcı olabilir. Sonuç olarak egzersiz terapisi uygulamaları daha etkili tedavi seçenekleri geliştirilmesine ve AH'nin ilerlemesinin yavaşlatılmasına, herhangi bir yan etki yapmaksızın yardımcı olabilir.

Anahtar Kelimeler: Alzheimer hastalığı, egzersiz terapisi, antioksidan enzimler, nöronal plastisite

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by vascular and neuronal dysfunction and cognitive regression (1, 2). The pathophysiology of AD is associated with different mechanisms such as genetic mutations, amyloid β (Aβ) burden, tau hyperphosphorylation, increased oxidative stress, neuroinflammation, neuroplasticity failure, neuronal loss, and synaptic degeneration (1-4) (Figure 1). Oxidative stress is an important underlying mechanism of neuronal loss that leads to a reduction in brain metabolism and an increase in mitochondrial damage (Figure 2).

Exercise is a non-pharmacological form of treatment for the prevention of AD and for slowing the progression of its symptoms (5-9). Recent studies have shown the beneficial effects of physical exercise on behavioral and psychological symptoms such as depressed mood and agitation, which are prevalent in AD. Not only the type of exercise but also its duration and frequency are unclear for the efficient prescription of exercise for AD. Although some studies have proposed that aerobic exercise for at least 30 min a few times a week has a beneficial role, the probable effects of resistance exercise and combined exercise are not yet known (10, 11).

Correspondence Author/Sorumlu Yazar: Dilek Özbeyli **E-mail/E-posta:** dilekozbeyli@yahoo.com
Received/Geliş Tarihi: 05.11.2016 **Accepted/Kabul Tarihi:** 07.12.2016 **Available Online Date/Çevrimiçi Yayın Tarihi:** 23.02.2017 **DOI:** 10.5152/clinexphealthsci.2017.230

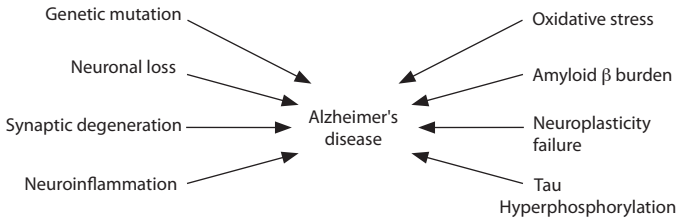

Figure 1. Mechanisms involved in the pathogenesis of Alzheimer's disease

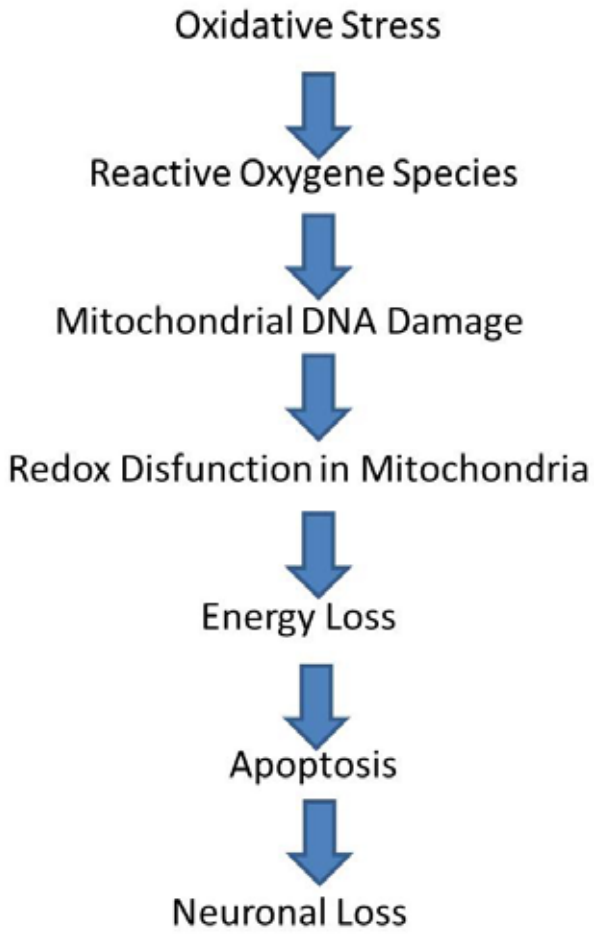

Figure 2. Mechanism of neuronal loss via oxidative stress

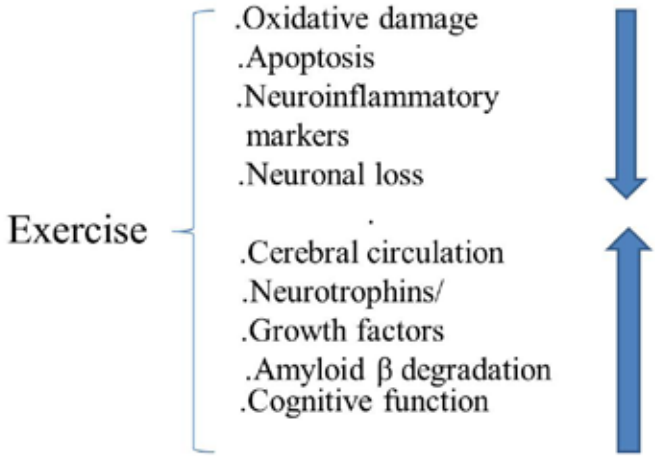

Figure 3. Underlying mechanisms of the beneficial effect of exercise on Alzheimer's disease

Table 1. Types of exercise

Types of Physical Exercise		
Flexibility	**Anaerobic**	**Aerobic**
Ballistic stretching	Lifting weights (resistance)	Walking
Dynamic stretching	Sprinting	Jogging
Proprioceptive neuromuscular facilitation	Rowing	Swimming
Static stretching	Sprinting activities	Hiking
Yoga	Tug of war	Playing tennis
	Jumping rope	Cycling
	Climbing	
	Sit-ups	
	Chin-ups	
	Isometrics	

Exercise Modalities

The term "physical activity" refers to actions that are produced via the consumption of energy by the striated muscles of the body. Physical activities are generally categorized into three types: flexibility (stretching) exercises, anaerobic (resistance/strengthening) exercises, and aerobic (cardiovascular) exercises (12-14) (Table 1). Flexibility exercises, such as dynamic and static stretching, improve the motion of muscles and joints. Aerobic exercises, such as swimming, running, walking, and cycling, are performed by larger muscle groups in the form of dynamic physical actions that require free oxygen and focus on increasing cardiovascular endurance (12, 14). It has been reported that regular aerobic exercise may lead to increases in the activity of antioxidant enzymes, improvements in angiogenesis, and upregulation in the synthesis of neurotrophic factors (7). Resistance exercises, such as weightlifting and jumping, which are also referred to as anaerobic exercises, are characterized by dynamic or static muscular contractions and are organized against manual or mechanical forces. Resistance exercises that use free weights increase muscle strength (12, 15). Regular resistance exercise is correlated with several positive adaptations such as increases in protein levels, enlarged cross-sectional areas of muscles, and elevated levels of insulin-like growth factor-1 (IGF-1) (16).

Underlying Mechanisms of the Effects of Different Exercise Modalities

There is no consensus about the best type of exercise for the amelioration of clinical outcomes in AD. A large number of studies have focused on the effect of aerobic exercise. Different mechanisms are known to mediate its beneficial effects (Figure 3). Aerobic exercise initially contributes to an increase in the levels of growth factors such as vascular endothelial growth factor, brain-derived neurotroph-

ic factor (BDNF), IGF-1, glial-derived neurotrophic factor, neuronal growth factor (NGF), and neurotrophin-3, all of which act in a synergistic manner to induce neuroplasticity and neurogenesis (7, 17-19). The growth factors then improve memory and cognitive functions via the stimulation of neurogenesis, synaptogenesis, neuroplasticity, and angiogenesis (7, 20, 21). Moreover, aerobic exercise increases cerebral blood flow and the levels of endothelial nitric oxide synthase and additionally decreases the levels of reactive oxygen species (ROS) in brain tissues, particularly in the hippocampus (7, 9, 21). Exercise-induced elevations in hippocampal cerebral blood volume were found to be associated with enhanced neurogenesis (22). Furthermore, in animal studies, improvements in cognitive functions after exercise have been shown in spatial learning memory, recognition memory, and contextual memory (23, 24). Aerobic exercise also increases cell survival and proliferation, upregulates Aβ clearance, decreases apoptotic cascades, and reduces $A\beta_{1-42}$ peptide levels in the rodent brain (25-27). Moreover, oxidative damage takes place initially in the brain of AD patients prior to the onset of Aβ deposition and plaque and neurofibrillary tangle formation (21). It is well known that regular swimming and running exercise reduce the production of ROS and upregulate antioxidant enzymes in different brain regions in rats (27, 28). Although an ameliorative effect of resistance exercise on any of the behavioral or biological signs of AD has not yet been reported, there is evidence that the prevalence of this disease is associated with a decline in muscle mass and muscle strength (28, 29). With reference to these data, it has been reported that resistance exercise may slow down the impairment of mobility and enhance balance in AD patients (30). In a similar way to the effect of aerobic exercise, levels of IGF-1 and BDNF have been shown to increase via resistance exercise (31, 32). In addition, there are numerous studies that reveal probable enhancements of cognitive functions after resistance exercise in elderly people (16, 31). Although the effect of a multicomponent exercise regimen that includes aerobic, balance, and strength training on AD is not known, it is shown to be particularly effective for improving motor and postural functioning and mitigating the risk of falling in AD patients (7, 33).

CLINICAL and RESEARCH CONSEQUENCES

Human and Animal Research Outcomes

Most of the present information about the mechanisms involved in the effects of exercise training has been obtained by animal studies of AD. It has been reported that regular swimming training, which is a well-known model of aerobic exercise, was able to protect against $A\beta_{1-40}$-induced neurotoxicity by decreasing short- and long-term impairments in object recognition memory by means of increasing the activity of antioxidant enzymes via decreasing the levels of neuroinflammatory markers in mouse models of AD (34). In addition, in a model of Aβ-induced AD, a decline in spatial memory and suppression of early long-term potentiation (E-LTP) and E-LTP-related signaling molecules such as phosphorylated Ca^{2+}/calmodulin-dependent protein kinase II (p-CaMKII), calcineurin (PP2B), and BDNF were observed in the hippocampus, and treadmill exercise, which is another model of aerobic exercise, had beneficial effects on E-LTP and memory performance by increasing levels of p-CaMKII, PP2B, and BDNF (35). Furthermore, it has been reported that even a light running exercise protocol increased cell survival and proliferation in transgenic mice and rat brain tissues (36). Related to this concern, it has also been reported that treadmill exercise inhibited apoptotic cascades, such as the caspase-9, cytochrome c, Bax, and caspase-3 cascades, in the brain tissues of transgenic mice (25, 27). Only a small number of articles concerning the effects of exercise on AD have demonstrated controversial results. Within the context of a meta-analysis, it has been shown that both combined (aerobic and non-aerobic) and aerobic exercise training, at both low and high intensities, had ameliorative effects on cognitive function. On the other hand, the same type of relationship between non-aerobic exercise training and cognitive functions was not found (37). Likewise, an 8-week program of resistance exercise training was found to be ineffective on cognitive functions (38). On the other hand, there is evidence that resistance exercise may be beneficial in AD. After resistance exercise, the serum concentrations of IGF-1 and BDNF were found to increase. Therefore, oxidative stress was demonstrated to be reduced and cognitive performance was shown to be improved in humans; further, the hippocampal expression of BDNF mRNA has been reported to be upregulated in rats (31, 32). Resistance exercise at moderate and high intensities for 24 weeks had advantageous effects on cognitive functions in elderly people (16). Resistance training significantly improved global cognitive scores, executive functions, and attention time in adults (39). It has been reported that resistance exercise has beneficial effects in older adults, increases the uptake of IGF-1 in the brain, insulin sensitivity, and cerebral blood flow, and decreases stress and depression (40). In addition to IGF-1, it is suggested that resistance training inhibits cognitive decline among elderly people via an increase in homocysteine levels (41). Moreover, strength or aerobic exercises may help increase independence in daily life activities and improve the physical ability of AD patients (33). These results have revealed that aerobic and resistance exercise therapies increase neurogenesis and neuroplasticity, act against brain alterations that occur during aging, and help to enhance cognitive functions and improve the quality of life of patients.

In animal studies, the Aβ load, which is a major sign of AD, has been reduced by exercise (26, 27). The main type of amyloid that accumulated in brain tissues has been reported to be $A\beta_{1-42}$ monomers. These monomers were formed by the clipping of amyloid precursor proteins (APPs) by beta and gamma secretases. When neuronal and astrocytic lysosomal and proteolytic degradation mechanisms are inadequate, $A\beta_{1-42}$ monomers become soluble and accumulate as oligomers of 2 to 6 peptides, which cause synaptic dysfunction (42). These soluble Aβ oligomers are regarded as major toxic species because their abundance is correlated with the intensity of synaptic dysfunction and neurodegeneration in AD (43). Studies based on describing the relationship between exercise and Aβ load mostly indicate aerobic exercise. In this context, Aβ load has been shown to be reduced by wheel running in transgenic mice (44). Furthermore, levels of soluble $A\beta_{1-42}$ in the hippocampus and cortex have been reduced by treadmill exercise in a dose-dependent manner. Moreover, the levels of Aβ-degrading proteins, such as matrix metalloproteinase-9, insulin-degrading enzyme, neprilysin, heat shock protein-70, and lipoprotein receptor-related protein-1, increased by treadmill exercise and have been revealed to be responsible for the upregulation of Aβ clearance (26). Besides, treadmill exercise for 5 weeks reduced the hippocampal microglial activity and Aβ levels but did not reduce plaque formation, and wheel running for 10 days reduced the expression of APP mRNA and Aβ levels but did not reduce plaque load in transgenic mice (45, 46). On the other hand, another study has shown that wheel running reduced the number of Aβ plaques and memory decline in transgenic mice (47). It has also been demonstrated in humans that physical activity has led to lower levels of Aβ in plasma and brain tissues (48, 49).

In our study group, different types of exercise, which were performed 3 days a week, had beneficial effects on the function of object recognition memory in an experimental rat model of AD, which was induced by D-galactose and ovariectomy. All types of exercise reduced oxidative stress by decreasing lipid peroxidation and increasing antioxidant status in rat brain tissues. Combined exercise has a stimulatory effect on NGF levels in the cortical part of the brain, which shows an improvement in neuroplasticity. The serum levels of IGF-1 increased by all exercise modalities. Elevated hippocampal levels of APP in the experimental model decreased with combined exercise, and the burden of Aβ was alleviated with all types of exercise in rat brain tissues. Consequently, our results suggest that different types of exercise attenuate the severity of AD (50).

CONCLUSION

Exercise leads to a significant improvement in cognitive functions and neuropathological markers related to AD. Because a large number of mechanisms of the pathogenesis of AD have been identified, it is clear that pharmacological treatment together with exercise therapies as a non-pharmacological form of treatment can succeed in inhibiting most mechanisms, in contrast to a treatment that targets only one mechanism. Adding exercise regimens to current treatments may lead to more effective treatment options and have benefits without any side effects.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University Animal Care and Use Committee (Decision No: 30.2014.mar).

Peer-review: Externally peer-reviewed.

Author contributions: Concept - D.Ö., Ö.K.Ç.; Design - D.Ö., Ö.K.Ç.; Supervision - D.Ö., Ö.K.Ç.; Resource - D.Ö., Ö.K.Ç.; Materials - D.Ö., Ö.K.Ç.; Data Collection and/or Processing - D.Ö., Ö.K.Ç.; Analysis and/or Interpretation - D.Ö., Ö.K.Ç.; Literature Search - D.Ö., Ö.K.Ç.; Writing - D.Ö., Ö.K.Ç.; Critical Reviews - D.Ö., Ö.K.Ç.

Acknowledgements: The authors would like to thank Prof. Dr. Berrak Yeğen and Prof. Dr. Göksel Şener for their support. The study has been originated from the doctoral thesis which was prepared in the Marmara University Health Sciences Institute (Investigations on mechanism of action of various exercise methods on cognitive functions in an experimental rat model of Alzheimer).

Conflict of Interest: : No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by a grant from the Marmara University Scientific Research Committee (BAPKO), SAG-C-DRP-050614-0228.

Etik Komite Onayı: Bu çalışma için etik komite onayı Marmara Üniversitesi Hayvan Deneyleri Yerel Etik Kurulu'ndan alınmıştır. (Karar No: 30.2014.mar).

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - D.Ö., Ö.K.Ç.; Tasarım - D.Ö., Ö.K.Ç.; Denetleme - D.Ö., Ö.K.Ç.; Kaynaklar - D.Ö., Ö.K.Ç.; Malzemeler - D.Ö., Ö.K.Ç.; Veri Toplanması ve/veya işlemesi - D.Ö., Ö.K.Ç.; Analiz ve/veya Yorum - D.Ö., Ö.K.Ç.; Literatür taraması - D.Ö., Ö.K.Ç.; Yazıyı Yazan - D.Ö., Ö.K.Ç.; Eleştirel İnceleme - D.Ö., Ö.K.Ç.

Teşekkür: Yazarlar Prof. Dr. Berrak Yeğen ve Prof. Dr. Göksel Şener'e desteklerinden dolayı teşekkür ederler. Bu çalışma Marmara Üniversitesi Sağlık Bilimleri Enstitüsü'nde yapılan bir doktora tezinden kaynaklanmıştır (Sıçanlarda Deneysel Alzheimer Hastalığı Modelinde Farklı Egzersiz Yöntemlerinin Kognitif Fonksiyonlar Üzerine Etki Mekanizmalarının İncelenmesi)**.**

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Bu çalışma, Marmara Üniversitesi Bilimsel Araştırma Projeleri Birimi tarafından (BAPKO- proje no: SAG-C-DRP-050614-0228) desteklenmiştir.

REFERENCE

1. Matura S, Carvalho AF, Alves GS, Pantel J. Physical exercise for the treatment of neuropsychiatric disturbances in Alzheimer's dementia: possible mechanisms, current evidence and future directions. Curr Alzheimer Res 2016; 13: 1112-23. [CrossRef]
2. Tramutola A, Lanzillotta C, Perluigi M, Butterfield DA. Oxidative stress, protein modification and Alzheimer disease. Brain Res Bull 2016; S0361-9230:30129-0.
3. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol 2015; 14: 388-405. [CrossRef]
4. Mesulam MM. A plasticity-based theory of the pathogenesis of Alzheimer's disease. Ann NY Acad Sci 2000; 924: 42-52. [CrossRef]
5. Mendiola-Precoma J, Berumen LC, Padilla K, Garcia-Alcocer G. Therapies for prevention and treatment of Alzheimer's disease. Biomed Res Int 2016; 2016:2589276. [CrossRef]
6. Spielman LJ, Little JP, Klegeris A. Physical activity and exercise attenuate neuroinflammation in neurological diseases. Brain Res Bull 2016; 125: 19-29. [CrossRef]
7. Paillard T, Rolland Y, de Souto Barreto P. protective effects of physical exercise in Alzheimer's disease and Parkinson's disease: a narrative review. J Clin Neurol 2015; 11: 212- 9. [CrossRef]
8. Farina N, Rusted J, Tabet N. The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review. Int Psychogeriatr 2014; 26: 9-18.
9. Archer T. Physical exercise alleviates debilities of normal aging and Alzheimer's disease. Acta Neurol Scand 2011; 123: 221-38. [CrossRef]
10. Matura S, Carvalho AF, Alves GS, Pantel J. Physical exercise for the treatment of neuropsychiatric disturbances in Alzheimer's dementia: possible mechanisms, current evidence and future directions. Curr Alzheimer Res 2016; 13: 1112-23. [CrossRef]
11. Thuné-Boyle IC, Iliffe S, Cerga-Pashoja A, Lowery D, Warner J. The effect of exercise on behavioral and psychological symptoms of dementia: towards a research agenda. Int Psychogeriatr 2012; 24: 1046-57. [CrossRef]
12. Plowman SA, Smith DL. Exercise Physiology: for Health, Fitness, and Performance. Fourth ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2014.
13. Prentice WE. Principles of Athletic Training: A compatency based approach. 15th. ed. New York: McGraw- Hill; 2003.
14. Pollock ML, Feigenbaum MS, Brechue WF. Exercise Prescription for Physical Fitness. Quest, 1995; 47: 320-37. [CrossRef]
15. Strickland JC, Smith MA. Animal models of resistance exercise and their application to neuroscience research. J Neurosci Methods 2016; 273: 191–200. [CrossRef]
16. Cassilhas RC, Viana VA, Grassmann V, Santos RT, Santos RF, Tufik S, et al. The impact of resistance exercise on the cognitive function of the elderly. Med Sci Sports Exerc 2007; 39: 1401-7. [CrossRef]
17. Revilla S, Suñol C, García-Mesa Y, Giménez-Llort L, Sanfeliu C, Cristòfol R. Physical exercise improves synaptic dysfunction and recovers the loss of survival factors in 3xTg-AD mouse brain. Neuropharmacology 2014; 81: 55-63. [CrossRef]
18. Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity - exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports Med 2010; 40: 765–801. [CrossRef]

19. Koo HM, Lee SM, Kim MH. Spontaneous wheel running exercise induces brain recovery via neurotrophin-3 expression following experimental traumatic brain injury in rats. J Phys Ther Sci 2013; 25: 1103-7. [CrossRef]
20. Kim TW, Choi HH, Chung YR. Treadmill exercise alleviates impairment of cognitive function by enhancing hippocampal neuroplasticity in the high-fat diet-induced obese mice. J Exerc Rehabil 2016; 12: 156-62. [CrossRef]
21. Radak Z, Hart N, Sarga L, Koltai E, Atalay M, Ohno H, et al. Exercise plays a preventive role against Alzheimer's disease. J Alzheimers Dis 2010; 20: 777-83.
22. Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A. 2007; 104: 5638-43. [CrossRef]
23. Griffin EW, Bechara RG, Birch AM, Kelly AM. Exercise enhances hippocampal-dependent learning in the rat: evidence for a BDNF-related mechanism. Hippocampus 2009; 19: 973-80. [CrossRef]
24. Gibbons TE, Pence BD, Petr G, Ossyra JM, Mach HC, Bhattacharya TK, et al. Voluntary wheel running, but not a diet containing (–)-epigallocatechin-3-gallate and beta-alanine, improves learning, memory and hippocampal neurogenesis in aged mice. Behav Brain Res 2014; 272: 131-40. [CrossRef]
25. Brandt MD, Maass A, Kempermann G, Storch A. Physical exercise increases Notch activity, proliferation and cell cycle exit of type-3 progenitor cells in adult hippocampal neurogenesis. Eur J Neurosci 2010; 32: 1256-64. [CrossRef]
26. Moore KM, Girens RE, Larson SK, Jones MR, Restivo JL, Holtzman DM, et al. A spectrum of exercise training reduces soluble Aβ in a dose-dependent manner in a mouse model of Alzheimer's disease. Neurobiol Dis 2016; 85: 218-24. [CrossRef]
27. Um HS, Kang EB, Leem YH, Cho IH, Yang CH, Chae KR, et al. Exercise training acts as a therapeutic strategy for reduction of the pathogenic phenotypes for Alzheimer's disease in an NSE/APPsw-transgenic model. Int J Mol Med 2008; 22: 529-39.
28. Ogonovszky H, Berkes I, Kumagai S, Kaneko T, Tahara S, Goto S, et al. The effects of moderate-, strenuous- and over-training on oxidative stress markers, DNA repair, and memory, in rat brain. Neurochem Int 2005; 46: 635-40. [CrossRef]
29. Hurley BF, Hanson ED, Sheaff AK. Strength training as a countermeasure to aging muscle and chronic disease. Sports Med 2011; 41: 289-306. [CrossRef]
30. Suttanon P, Hill KD, Said CM, Williams SB, Byrne KN, LoGiudice D, et al. Feasibility, safety and preliminary evidence of the effectiveness of a home-based exercise programme for older people with Alzheimer's disease: a pilot randomized controlled trial. Clin Rehabil 2013; 27: 427-38. [CrossRef]
31. Portugal EM, Vasconcelos PG, Souza R, Lattari E, Monteiro-Junior RS, Machado S, et al. Aging process, cognitive decline and Alzheimer`s disease: can strength training modulate these responses? CNS Neurol Disord Drug Targets 2015; 14: 1209-13. [CrossRef]
32. Lee MC, Okamoto M, Liu YF, Inoue K, Matsui T, Nogami H, et al. Voluntary resistance running with short distance enhances spatial memory related to hippocampal BDNF signaling. J Appl Physiol 2012; 113: 1260-6. [CrossRef]
33. Rao AK, Chou A, Bursley B, Smulofsky J, Jezequel J. Systematic review of the effects of exercise on activities of daily living in people with Alzheimer's disease. Am J Occup Ther 2014; 68: 50-6. [CrossRef]
34. Souza LC, Filho CB, Goes AT, Fabbro LD, de Gomes MG, Savegnago L, et al. Neuroprotective effect of physical exercise in a mouse model of Alzheimer's disease induced by β-amyloid$_{1-40}$ peptide. Neurotox Res 2013; 24: 148- 63. [CrossRef]
35. Dao A, Zagaar MA, Levine AT, Salim S, Eriksen J, Alkadhi KA. Treadmill exercise prevents learning and memory impairment in Alzheimer's disease-like pathology. Curr Alzheimer Res 2013; 10: 507-15. [CrossRef]
36. Patten AR, Sickmann H, Hryciw BN, Kucharsky T, Parton R, Kernick A, et al. Long-term exercise is needed to enhance synaptic plasticity in the hippocampus. Learn Mem 2013; 20: 642-7. [CrossRef]
37. Groot C, Hooghiemstra AM, Raijmakers PG, van Berckel BN, Scheltens P, Scherder EJ, et al. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. Ageing Res Rev 2016; 25: 13-23. [CrossRef]
38. Ruiz JR, Gil-Bea F, Bustamante-Ara N, Rodríguez-Romo G, Fiuza-Luces C, Serra-Rexach JA, et al. Resistance training does not have an effect on cognition or related serum biomarkers in nonagenarians: a randomized controlled trial. Int J Sports Med 2015; 36: 54-60.
39. Fiatarone Singh MA, Gates N, Saigal N, Wilson GC, Meiklejohn J, Brodaty H, et al. The Study of Mental and Resistance Training (SMART) study— resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. J Am Med Dir Assoc 2014; 15: 873-80. [CrossRef]
40. Gates NJ, Valenzuela M, Sachdev PS, Singh NA, Baune BT, Brodaty H, et al. Study of Mental Activity and Regular Training (SMART) in at risk individuals: A randomised double blind, sham controlled, longitudinal trial. BMC Geriatr 2011; 11: 19. [CrossRef]
41. Liu-Ambrose T, Donaldson MG. Exercise and cognition in older adults: is there a role for resistance training programmes? Br J Sports Med 2009; 43: 25-7. [CrossRef]
42. Elmacı NT. Alzheimer hastalığının patofizyolojisi. Turkiye Klinikleri J Neurol-special Topics 2012; 5: 3.
43. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat Rev Mol Cell Biol 2007; 8: 101-12. [CrossRef]
44. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. J. Neurosci 2005; 25: 4217-21. [CrossRef]
45. Ke HC, Huang HJ, Liang KC, Hsieh-Li HM. Selective improvement of cognitive function in adult and aged APP/PS1 transgenic mice by continuous non-shock treadmill exercise. Brain Res 2011; 1403: 1-11. [CrossRef]
46. Mirochnic S, Wolf S, Staufenbiel M, Kempermann G. Age effects on the regulation of adult hippocampal neurogenesis by physical activity and environmental enrichment in the APP23 mouse model of Alzheimer disease. Hippocampus 2009; 19: 1008-18. [CrossRef]
47. Yuede CM, Zimmerman SD, Dong H, Kling MJ, Bero AW, Holtzman DM, et al. Effects of voluntary and forced exercise on plaque deposition, hippocampal volume, and behavior in the Tg2576 mouse model of Alzheimer's disease. Neurobiol Dis 2009; 35: 426-32. [CrossRef]
48. Brown BM, Peiffer JJ, Taddei K, Lui JK, Laws SM, Gupta VB, et al. Physical activity and amyloid-β plasma and brain levels: results from the Australian imaging, biomarkers and lifestyle study of ageing. Mol Psychiatry 2013; 18: 875-81. [CrossRef]
49. Liang KY, Mintun MA, Fagan AM, Goate AM, Bugg JM, Holtzman DM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. Ann Neurol 2010; 68: 311-8. [CrossRef]
50. Özbeyli D. Sıçanlarda Deneysel Alzheimer Hastalığı Modelinde Farklı Egzersiz Yöntemlerinin Kognitif Fonksiyonlar Üzerine Etki Mekanizmalarının İncelenmesi. M.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2016.