DERLEME REVIEW

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Which Exercise Type is Better on Autophagy in Older Adults?

Yaşlı Bireylerde Hangi Egzersiz Türü Otofaji İçin Daha İyidir?

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ABSTRACT Aging is characterized by accumulation of damage in cellular components increasing fragility and risk of death caused by disruption of different biological processes. The autophagy is a basic cellular homeostasis process requiring different pathophysiologic conditions for degradation and recycling of damaged cellular organelles and proteins. This process, called autophagy, is a fundamental cellular homeostatic process required in different pathophysiological conditions for the degradation and recycling of damaged cellular organelles and proteins. During the aging process, the autophagy flux reduces. However, both animal and human studies show that exercise has positive effects on autophagy markers and flux within aging metabolism. The aim of this review is to answer a few questions such as "Which exercise stimulates autophagy more in aging?", "What do the available human research results indicate?", "How does aging affect autophagy?", "What is the correlation between exercise, aging, autophagy and muscle mass?". According to the research results, resistance exercises and endurance exercises affect autophagy in the aging process. Resistance exercises increase the autophagy flux and may prevent sarcopenia. Endurance exercises increase oxidative stress, which may increase autophagy flux and preserve mitochondria quality. There is a need for new studies to more clearly reveal the effects of both exercise types. However, it is well known at present that whatever exercise is performed, obesity, chronic diseases, menopause, initial autophagy level and content, fitness levels of elderly individuals, training status, mitochondria content, muscle mass and nutrition type may change the progress of autophagy.

Keywords: Autophagy; aging; exercise; sarcopenia; cell; mitochondria

ÖZET Yaşlanma, farklı biyolojik süreçlerin bozulmasından kaynaklanan kırılganlığı ve ölüm riskini artıran hücresel bileşenlerde hasar birikimi ile karakterizedir. Hücre içinde meydana gelen yıkım olayları sayesinde organizmanın ihtiyacının kalmadığı hasara uğramış organeller, sitoplazmik parçalar ve birikmiş proteinler ortadan kaldırılır. Otofaji olarak adlandırılan bu süreç, hasarlı hücresel organellerin ve proteinlerin bozulması ve geri dönüşümü için farklı patofizyolojik koşullarda gerekli olan temel bir hücresel homeostatik süreçtir. Yaşlanma sürecinde otofaji akışı azalmaktadır. Fakat hem hayvan hem de insan çalışmaları, yaşlanan metabolizma üzerinde egzersizin otofaji belirteçleri ve akışı üzerindeki olumlu etkileri olduğunu göstermektedir. Bu derlemenin amacı; "Yaşlanmada hangi egzersiz otofajiyi daha çok harekete geçirir?" "Mevcut insan araştırmalarının sonuçları neyi işaret etmektedir?", "Yaşlanma otofajiyi nasıl etkiler?", "Egzersiz, yaşlanma, otofaji ve kas kütlesi arasındaki ilişki nedir?" sorularını mevcut araştırmalara göre yanıtlamaktır. Araştırma sonuçlarına göre direnç egzersizleri ve dayanıklılık egzersizleri, yaşlanma sürecindeki otofajiyi etkiler. Direnç egzersizleri otofaji akışını artırarak, sarkopeniyi önleyebilir. Dayanıklılık egzersizleri, oksidatif stresi artırarak, otofaji akışını artırabilir ve mitokondri kalitesini koruyabilir. Her iki egzersiz türünün etkilerinin daha net ortaya çıkarılması için yeni çalışmalara ihtiyaç vardır. Ancak şu anda iyi bilinmektedir ki hangi egzersiz yapılırsa yapılsın, obezite, kronik hastalıklar, menopoz, başlangıç otofaji düzeyi ve içeriği, yaşlı bireyin kondisyon düzeyi, antrenman durumu, mitokondri içeriği, sahip olduğu kas kütlesi ve beslenme türü otofajinin seyrini değiştirebilecektir.

Anahtar Kelimeler: Otofaji; yaşlanma; egzersiz; sarkopeni; hücre; mitokondri

Autophagy and healthy aging are new research areas that have not yet been fully discovered. Therefore, in this review have been focused on three questions related to the topic. How does aging affect autophagy? Is there relationship between exercise, aging, autophagy and muscle mass? What type of exercise increases autophagy markers or flux more in the older adults?

"**Aging**" is characterized by accumulation of damage in cellular components increasing fragility and risk of death caused by disruption of different biological processes.[1] Recently there has been an increase in the older adults in society and life expectancy has increased.[2] In spite of the increase in life length, the increase in diseases like cardiovascular diseases, diabetes, obesity, insulin resistance, and

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hypertension have caused significant increases in early aging and a shortening of life span. The reasons for aging continued to be explained by a variety of theories like DNA injury, oxidative stress, telomer shortening and apoptosis. Though attempts are made to delay it with pharmacologic treatment methods, aging cannot be reversed and no radical delaying effect can be seen. In addition to medication treatments, exercise plays an important role in delaying aging. Changes in lifestyle delay early aging and improve cardiovascular health, functional fitness and health-related physical fitness parameters.[3-5]

Due to destructive events occurring in the cell, damaged organelles, cytoplasmic fragments and accumulated proteins that the organism no longer requires are removed.[6] This process called "**autophagy**" is a basic cellular process involved in protein and organelles degradation, also, is a basic cellular homeostasis process required in different pathophysiologic conditions for recycling. The term "**autophagic flux**" represents the whole process of autophagy rather than measurement of the number/volume of autophagic parameters. With advancing age, autophagic functions in many organs and tissues are disrupted. This situation limits the cells ability to keep a healthy proteome and organelles causing loss of cellular functions and cell deaths. The result is that older adults have fewer defenses against cellular stress and pathogens, and energy means they cannot adapt to difficult conditions.[7] In addition to this, with advancing age there is a clear reduction in autophagy markers, a decrease in autophagic ability of skeletal muscle and finally it is clear that autophagy dysfunction increases speed with aging.[8-14] Autophagy uses damaged cellular components to restructure cellular structures, to degrade lysosomal nutrition stores and at the same time plays an considerable role in ageing and exercise, ensuring survival in response to nutritional deficiency in cells or to intracellular pathogens and is a mechanism protecting organisms from yeasts to mammals.[15] Additionally, it is considered to undertake a cleaning function to protect the integrity of organelles in the cell and is active in most cell types even at basic level.[16]

Some studies indicated that the main role of autophagy is to keep cells viable under stress conditions. As stress factors, exercise or physical activity play large roles.[17] In fact, the connection of exercise with autophagy first began to be researched in 1984.[18] However, the relationship between exercise with the autophagy flux in the aging organism is still not fully known. Though most studies are mouse experiments, human studies are increasing. Research in recent times show the actual source of benefits of exercise and calorie limitation in cardiovascular aging are believed to be the preservation at high rates of the autophagy process to cleaning long-lived and damaged organelles.[3] Exercise improves general health and autophagy and reduces cardiovascular risk. Additionally, resistance training, continuous endurance training and interval training appear to improve telomerase activity, telomer length, cellular aging, autophagic flux, autophagy markers, regenerative capacity and healthy aging in recent studies. However, these data support the idea that exercise will not do the same for aging.[19] Research about which exercise type is more effective on autophagy in aging still continues.[20]

MATERIAL AND METHODS

SELECTION CRITERIA OF THE STUDIES

The articles for this review; (1) were published in peer-reviewed international journals; (2) were available in full-text; (3) studied in human and above 65 years old for the second and the last stages; and (4) were about resistance or strength and endurance or aerobic exercises. The articles which (1) could be for full text or were not full text; (2) were studied in animal subjects for the second and the last stages; (3) did not include 65 years old subjects; and (4) were not about resistance or strength and endurance or aerobic exercises were excluded.

STUDY STAGES AND PROCESS

First, key words were determined. Always two or more keywords were used in different combinations. The review was completed on three stages. The first one was general research stage. "Autophagy" and "Aging" or "Older adults" and "Autophagic flux" were used as keywords in animal and human studies. The second one was focused on exercise and autophagy subjects which "Exercise" and "Muscle

mass" and "Older adults" or "Elderly" or "Aging" were used as keywords in older (above aged 65 years old) human studies. The last one was focused on differences and advantages or disadvantages of exercise type on autophagy. For this stage "Strength exercise" or "Resistance exercise" and "Endurance exercise" or "Aerobic exercise" and "Aging" or "Elderly" were used as keywords in human studies conducted with older (above aged 65 years old) subjects.

METHODOLOGICAL QUALITY ASSESSMENT

A total of 980 articles were found in selection criteria by authors for all stages. All articles were divided to date categories for first read. The category ranges were January 2020-2017 years; 2016-2013 years; 2012 and oldest. At the end of categories process, for the quality assessment, studies were reviewed by three authors separately. If the one author noted different study result, the study was assessed by the other author. At the end of the re-read process, the references section and full review were checked by three authors. For the first stage 45 articles in selection criteria were assessed for the second stage 14 articles were assessed and the last stage 29 articles were accessed. Totally 83 articles were included for this review.

RESULTS

THE RELATIONSHIP BETWEEN AUTOPHAGY, AGING, MUSCLE MASS AND EXERCISE

Autophagy is known to preserve muscle mass and at the same time increases functional muscle power. Though exercise plays a role in regulating autophagy in some tissues, the actual point of focus is skeletal muscle and it is necessary for the integrity of muscle. Autophagy activation during physical activity contributes to maintaining skeletal muscle homeostasis and increases satellite cells.[21-23] Additionally, it assists in preserving muscle fibril strength renewed by satellite cells and muscle mass. Many studies to date have shown that autophagy preserves muscle mass and additionally increases functional muscle power, with protective duties against many stress factors like intensive exercise, oxidative stress, hypoxia and infection.[24-28] Autophagy may be a regulator of stem cells in sarcopenia reversing the aging in satellite cells and regulating renewal activity. This shows that autophagy controls the molecular activity necessary for differentiation of stem cells.[29,30]

During exercise, autophagic flux is stimulated in human skeletal muscle and this process is linked to the intensity of exercise rather than nutrition.[31] In spite of these positive effects, the role of autophagy in human muscle mass is still not clear. In fact, some studies have stated that excessive increase in autophagy activity has destructive effects and weakens muscles; however, autophagy maintained at basal level is beneficial for homeostasis of muscle.[32,33] The maintenance of this homeostasis may be beneficial in ensuring the possibility of using amino acids involved in recycling as alternative energy substrates.[34] Autophagy stimulates the transition of satellite cells from passive to active and autophagy may support the subcellular organelles required during satellite cells activation. This process becomes dysfunctional in stages during aging in skeletal muscle in rodents and humans. The research results indicate differences in the autophagic response in muscles according to the duration and intensity of exercise, satiety/starvation status and muscle fiber types participating in activity.[7,35,36] It was identified in previous research that high intensity exercise increases autophagic flux more.[31] This indicates that the process is directed by the intensity of exercise rather than the duration of exercise. However, there is a need for new research to reveal this distinction better in humans. Autophagy completes basic functions like energy support of skeletal muscle and recycling components. However, in the older adults due to multiple factors like accumulation of misfolded proteins or dysfunctional mitochondria, autophagy formation in skeletal muscle may be prevented. For repair of muscular injury, exercise is necessary to stimulate autophagy ensuring muscle adaptation, fiber-type change, preservation of muscle mass and interaction of satellite cells. However, it is still not fully known what situations change the mechanism of this stimulation between the older and adults.

Aging speeds up the loss of skeletal muscle called "**sarcopenia**". As a result, the relationship between autophagy and sarcopenia in aging is impor-

tant for muscle integrity. The muscle manages not just exercise, but also metabolism, circulation, and cognitive functions, so sarcopenia threatens a healthy life. In older population, the incidence of sarcopenia increases.[37] During muscle contraction and afterwards, injured structures are continuously removed and renewed; as a result, some adaptations provided by regular exercise have vital importance for healthy working of autophagy. Autophagy is thought to cause both wanted and unwanted responses in the system during exposure to mechanical stress during exercise and to the transition to denervated muscle. In older adults, sustaining autophagic flux at optimum levels will protect against sarcopenia. Other factors that are responsible for increase of sarcopenia in this process may be endurance exercises and sedentary lifestyles.[38] Contrary to this, exercise as a process linked to basal autophagy is the best available treatment to slow sarcopenia in aging and improve mitochondria quality and calm satellite cell numbers.[39,40] Also, high-intensity interval training (HIIT) and resistance exercises promote satellite cells pool expansion in older adults.[41] The endurance and resistance exercise may reverse the unwanted effects due to autophagy damaged by sarcopenia.[42-44]

As a result, we can understand clearly from animal and human studies that the exercise affects autophagy markers and flux in aging metabolism positively. However, these results may be negative considering sarcopenia. In fact, some exercise types may increase autophagic flux in individuals; however, they may bring unwanted results for sarcopenia. Below, attempts are made to answer the questions "Which exercise in aging activates autophagy most?" and "What do the results of available human research indicate?".

THE EFFECT OF RESISTANCE EXERCISE ON AUTOPHAGY IN OLDER ADULTS

"**Resistance exercise**" is effective in increasing muscle mass. However, it is known that protein synthesis is more inefficient in older adults compared to youths.[45] In spite of insufficiency due to metabolism in young and older, resistance exercises are beneficial and recommended for older adults in many situations like daily life activities, preserving muscle mass and power, improving basic functions and reducing risk of falls. Now the topic of curiosity is the effect of resistance exercise on autophagic flow of older adults. Autophagy induced by resistance exercise in older animal and humans cleans unwanted proteins from the environment and may be a protective intervention against sarcopenia. According to the first study results, the treadmill exercise is thought to regulate the age-linked weakening of proteins linked to autophagy and preserve muscle mass.[42] Different protein synthesis mechanisms between age groups increase our expectation that there will be different autophagy development results linked to resistance exercise. However, according to research results, acute resistance exercises have the same effect on autophagy interaction and muscle protein destruction in young and older adults. This result, of course, leads to the consideration that it may be linked to exercise type, in addition to nutrition and initial autophagy dysfunction level. The same study found that protein destruction markers increased and autophagy reduced after acute resistance exercise in both young and the older adults.[46] In conclusion, autophagy markers increase with different types of exercise.[21,47-49] However, the some results about initiation of autophagy in skeletal muscle during aging process are inconsistent.[14,50-53] In a previous study, sarcopenia was indicated to disrupt the critical stimulant of autophagy.[54]

In spite of these contradictions, resistance exercises to keep muscle mass during aging stimulate autophagy.[43] Many studies support the view that the increase in muscle mass and function caused by resistance exercise is through mobilizing the autophagy pathway.[37] Resistance exercises increase autophagy activity, reduce muscle mass and develop muscle power and are stated to be beneficial for aging muscle tissue. While endurance exercises cause metabolic adaptation in skeletal muscle, resistance exercises provide to increasing muscle mass. Thus, the autophagy activity induced by exercise improves muscular performance and sarcopenic phenotype. Autophagy activity in aging plays important roles in differentiation of satellite cells and in adaptation of muscle mass. However, autophagy stimulated by ox-

idative stress or calorie limitation may not be beneficial for skeletal muscle homeostasis. Catabolic paths may be more dominant than the anabolic processes occurring with aging.[37] One of these processes of diseases linked to menopause in older women may increase further with the prevalence of high immobility. For all that, the relationship between exercise and muscle autophagy in situations with deficient estrogen is still not clear.

Resistance exercise for 8 weeks in older adults from 69-75 years of age was investigated for the effect in preventing age-linked falls in autophagy, low-grade inflammation and apoptosis. Before and after exercises, participants had maximum strength of arm, leg and chest determined and blood samples taken. The experimental group was identified to have increases in the autophagic flux markers of LC3II/LC3I; but, this was not significant. There was no change in the control group. Finally, in this study, 8 weeks of resistance training was shown to cause autophagy mechanism activation in peripheral blood mononuclear cells in older adults.[55]

Autophagy conducts long-lived proteins and damaged organelles to the lysosome and destroys them and is a catabolic process preserving the cell. As a result, autophagy performs as an active recycling system to preserve homeostasis balance and cellular renewal that can be regulated with exercise. The ability to repair damaged tissues and to respond to continuous stressful stimulants is based on preserving all body functions during life. The common view is that autophagy is a key process causing variable functional reductions in older cells. Autophagy is not a regulator developing cellular functions. However, it plays a continuous central and important role, especially in aging. Mitochondria quality control and increase in function markers is not linked to chronologic age. It may be improved by regular exercise. Some findings show that physically-active people have higher mitochondrial fission and mitophagy in skeletal muscles.[56] Two studies investigating the autophagosome content in skeletal muscle in the first hour after ending resistance exercises stated the effect of resistance exercises on autophagy.[46,57] In conclusion, resistance exercise in humans is an effective strategy to increase skeletal muscle mass and power in the older adults and at the same time was shown to regain type II muscle fiber satellite cell content to young adult levels.[58]

THE EFFECT OF ENDURANCE EXERCISE ON AUTOPHAGY IN OLDER ADULTS

Endurance exercise is an exercise type frequently used to preserve the cardiovascular system health or aerobic capacity of older adults. Additionally, older person uses high energy in endurance exercise, especially in exercise at high intensity. Also, it may cause production of reactive oxygen species (ROS) which may harm mitochondria and metabolic discomfort.[59] Therefore, it may important play a role in selective removal of flawed mitochondria, development of resistance against oxidative stress and potential inflammation, removal and recycling of flawed mitochondria during exercise.[59-61] According to previous research results, 60 minutes or more of 55-70 % VO2max intensity aerobic exercise is known to stimulate autophagic activity in skeletal muscle.[31,47,62,63] Another study identified that during long-duration endurance exercise, trained athletes had increases in autophagy markers and related proteins.[47,62] Recreational bicycle training with ~50% VO2max and 55%-70% VO2peaks for 60-120 minutes increased autophagy.[31,63] Additionally, endurance exercise may suppress the apoptotic pathway in skeletal muscle and aerobic exercise and was stated to assist in maintaining autophagy protein expression.[64,65] In fact, it was identified to even increase expression of proteins linked to autophagy in skeletal muscle.[66] With the support of the research results, we can conclude that, both acute and chronic endurance exercise triggers stimulation of the autophagy.[31,59,62,67] Additionally, the situation may be different in obese elderly people. Colleluori et al. stated that anabolic resistance and disrupted myocellular quality may increase age-linked sarcopenia made more severe by obesity.[68] Combined exercise (aerobic and resistance) in weight-loss programs for obese older people was identified to reduce expression of autophagy markers by more than aerobic exercise. As a result, in obese older people, combined exercise (aerobic and resistance) appears to be more beneficial to improve muscle protein synthesis and myocellular quality than separately performed re-

sistance and aerobic exercise. Thus, muscle mass will be preserved during weight-loss treatment.

The research about changes in autophagy flux after endurance exercise in older adults is limited. Aerobic exercise continuing for 8 weeks caused higher expression of autophagy in peripheral blood molecular cells in older adults. This result expands information about previously-determined benefits of exercise in the elderly population and autophagy adaptation linked to exercise in humans and is considered to be an important factor explaining the relationship between exercise type and autophagy.[9]

According to Mancini et al., lifelong football training prevents damaged protein accumulation in skeletal muscle in older adults in general and ensures a more efficient protein quality control process in autophagy.[69] This increases life expectancy. According to these research results, continuation in long-term sports branches will contribute to autophagy in older adults. Life-long football training was seen to induce transcriptional activation of key markers related to improving interval metabolism and cardiovascular capacity of older veteran football players compared to participants without training in protein quality control pathways, especially those included in autophagy. There is strong evidence that developed autophagy delays aging and lengthens life. Increasing autophagy prevents accumulation of age-linked protein aggregates and damaged organelles in cells.[70] Older adults with 30 years of regular exercise had preserved fiber morphology and calcium processing and better mitochondria organization including intracellular organelle infrastructure and ATP production compared to healthy sedentary elderly people and had reduced expression of genes related to autophagy and ROS.[71]

In spite of some debate, acute endurance exercise was shown to activate autophagy in skeletal muscle tissue, just as in other tissues.[21,47,49,72] Masschelein et al. proposed the effect of exercise on autophagy may vary linked to the history of widespread autophagic flux.[64] Aging disrupts the lysosomal autophagy and ubiquitin-proteasome systems playing a central role in cellular proteostatic mechanisms.[73,74] Following endurance exercise the known autophagy activator of 5-AMK and activated protein kinase (AMPK) are well-known to increase within skeletal muscle.[75] It is important to understand the difference between endurance and resistance exercises and how it affects individual skeletal muscle autophagy. Endurance exercise results in a large increase in AMPK, while resistance exercise increases mTOR levels. This simple difference may change the initiation or reduction path of autophagy with different exercise forms.[76] Aerobic exercises stimulate autophagy; thus, IGF-1, protein kinase B (Akt)/mTOR/forkhead O3A signal pathways are modulated preventing strength and muscle mass loss, and eliminating harmful proteins triggering neurodegeneration.[42,43,72] Aging and aerobic exercise appear to have limited effect on autophagy and apoptosis markers in human skeletal muscle.[77] Studies have shown that endurance exercise may stimulate adaptation of apoptosis-linked proteins.[78] Autophagy disorder severely affects adaptation of muscle tissue to endurance exercise.[72,79-81]

To date, the autophagy response to endurance exercise has been researched most. Endurance exercise increases autophagy; however, it reduces the cross-sectional area of muscle. Thus, it develops adaptation to exercise providing better oxygen diffusion. Additionally, physically-active older adults have increased mRNA levels of autophagy markers like Beclin-1, ATG7 and p62 and additionally mitophagy markers like BNIP3 and parkin in muscle.[82,83]

WHICH ONE IS BETTER EXERCISE TYPE ON AUTOPHAGY IN OLDER ADULTS?

In conclusion, resistance exercise and endurance exercise affect autophagy during the aging process. Resistance exercise increases autophagic flux and may prevent sarcopenia.[84] Endurance exercises increase oxidative stress and may increase autophagic flux and preserve mitochondria quality. Excessive autophagic flux may lead to unwanted outcomes in the older organism. Research investigating the effect of exercise on autophagy in older women and men is very limited. Probably the autophagy process in the genders may be affected at different levels by exercise linked to oxidative stress, menopause, andropause, mitochondria amount, muscle mass and fat mass. There is a need for new studies to more clearly reveal the effect of both types of exercise. However, it is well known at the mo-

ment, that whatever exercise is performed, obesity, chronic diseases, menopause, initial autophagy level and content, fitness of elderly individuals, training status, mitochondria content, muscle mass and nutritional type may change the course of autophagy. Care should be taken when selecting exercise for older adults.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gülşah Şahin;* ***Design:*** *Gülşah Şahin;* ***Control/Supervision:*** *Gülşah Şahin;* ***Data Collection and/or Processing:*** *Gülşah Şahin, Bilgetekin Burak Günar, Ali Coşkun;* ***Analysis and/or Interpretation:*** *Gülşah Şahin;* ***Literature Review:*** *Gülşah Şahin, Bilgetekin Burak Günar, Ali Coşkun;* ***Writing the Article:*** *Gülşah Şahin, Bilgetekin Burak Günar, Ali Coşkun.*

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