

The Effect of Physical Activity on Adipose Tissue and Skeletal Muscles: A Literature Review

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Abstract

Introduction: The importance of changing the color of white adiposities into brown is due to the fact that it can have anti-obesity and anti-diabetic effects by adjusting energy balance (by converting storage form into energy consumption). The purpose of this study was to investigate the effect of physical activity on adipose tissue and skeletal muscles.

Methods: In this review, were searched online databases including Google Scholar, SID and PubMed, Science Direct and Scopus using the following keywords: "Training", "Exercise", "Physical activity", "Mayokin", "Adipose tissue", "Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α)", "Fibronectin type III domain-containing protein 5 (FNDC5)", "Irisin" and "Uncoupling proteins 1 (UCP-1)". All articles including research studies, review articles, descriptive and analytical studies, and cross-sectional research, published during 1998-2017, were reviewed.

Results: Based on our literature review, physical exercise can be effective as an adipose tissue activated agent in the prevention and treatment of obesity. In this regard, irisin seems to be influenced by a variety of sports activities and is a significant factor in the conversion of white to brown adipose tissues and can play a role in weight loss and increase the body thermogenesis.

Conclusion: According to these studies, the expression of irisin and FNDC5 converts white adipose into brown adipose and increases the energy consumption. Regular exercise training on preventing obesity, diabetes and its complications, and improving health have already been proven; but the point is that these beneficial effects are due to the cellular-molecular mechanism is still under discussion.

Keywords: Exercise, Mayokin, PGC-1 α , Irisin

Introduction

Physical activity is one of the main factors for reinforcing health and prevention of some diseases that can directly increase energy consumption and indirectly affect the regulation of energy intake and the cost of energy by altering the secretion of the involved hormones (1). Most studies emphasize the usefulness of endurance training on the health development and prevention of metabolic disorders. Based on the findings, these exercises lead to many morphological and metabolic adaptations such as increased mitochondrial biogenesis and increased total fat oxidation capacity in skeletal muscle (2). Also, research results indicate that resistance exercises can also lead

to in numerous physiological adaptations. Therefore, the recognition of molecular cellular mechanisms caused by the response to sport training, especially weight training exercises and changes in white and brown adipose tissue, is one of the most important parts of the thermogenesis regulation, which requires more studies. Nevertheless, the positive effects of exercise on cellular and molecular mechanisms have not been well known as well (3). Therefore, one of the most important challenges is the identification of the mechanisms of the quasi-drug effects of the exercise. One of the characteristics of exercise effects is the conversion of white adipose tissue into brown adipose tissue. These physiological changes mean that

exercise increases the relative fat content of brown tissue (3). The skeletal muscle, such as the endocrine, plays an important role in metabolic activities of homeostasis, and has the ability to communicate with the adipose tissue, the liver and the brain (4). One of these effective markers is Irisin, which is released as a result of muscle contraction and its target tissue is adipose tissue (4). Irisin is a protein with a molecular weight of 12 kDa, which consists of 112 amino acids, and is referred to as a source of muscle hormone secretion. Irisin is the product of the breakdown of membrane protein fibronectin, which is found mainly in the muscle tissue of humans and rats and can then be released into the plasma (5). The gene expression of membrane protein of Fibronectin domain containing or FNDC5 increases through peroxisome proliferator-activated receptor gamma (PPAR γ) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a) mediators. The FNDC5 gene is encoding uncoupling proteins type 1 (UCP1) agent; this action increases with muscle activity and affects the process of irisin construction. The irisin release pattern is similar to that of other membrane polypeptides, such as epidermal growth factor and alpha transforming growth factor (5). The irisin increases the oxidation of fatty acids and creates heat by increasing the expression of the UCP1 gene in white adipose tissue. On the other hand, irisin increases the heat and improves energy consumption, glucose homeostasis and ultimately weight loss by changing the white adipose tissue to brown, (5). Therefore, irisin can be considered as a preventative agent for the treatment of obesity and metabolic diseases. Although many studies are being conducted on irisin so far, the subject of the physiological functions of irisin in the human body and the effect of physical exercises, especially aerobic exercises with different intensities, on its expression is ambiguous (6). Therefore, before using physical exercises as a non-pharmacological treatment and giving a definitive opinion about

its positive effects, further investigation is needed. Various studies have shown that physical activity and exercise increase the expression of PGC-1a gene (7, 8). In this regard, Bostrom *et al.* (2012) reported that three weeks of endurance training on moderate treadmill lead to doubling of UCP-1 gene expression of visceral adipose tissue and its 25-fold increase in sub-abdominal adipose tissue. Also, the implementation of 10 weeks of endurance training result to doubling of muscle FNDC5mRNAs and UCP1mRNA in subcutaneous adipose tissue (3). From the findings of this study, it can be concluded that exercise is one of the most important factors influencing the secretion of Irisin hormone and energy metabolism (9, 10). However, there is no uniform opinion about the nature and type of exercise, its severity and its effective duration on the development of physical health (11). In the meantime, the importance of some types of resistance weight training exercises is that the metabolic adaptations to this type of sports activity through the mediation of the signaling path can be approximately the same as the endurance training adaptations (9). However, despite the many benefits of traditional endurance training, many adults do not participate in these exercises because they do not have enough time. Therefore, participating in the high intensity interval training (HIIT) as an affordable and effective protocol for increasing the level and activity of the signaling pathway of the adipose tissue phenotype and reducing the body fat percentage of overweight individuals was considered by the researchers. The apparent characteristic of these exercises is its very low volume compared to continuous exercises (12). In addition, in most studies, the intensity of exercise activity is a major factor affecting the level and activity of SIRT1, PGC1a (12). However, there is little information about the oxidative state after HIIT exercises. The time of doing intensive exercises can be effective in promoting a person's metabolic level to a large extent, which cannot be easily achieved in

moderate, sustained endurance exercises. In this regard, Little *et al.* (2010) reported that performing HIIT exercises for 2 weeks increased the expression of PGC1 α gene and SIRT1 levels in the muscle, but did not change the level of PGC1 α protein. HIIT training can be a strong stimulant to increase SIRT1 and PGC1 α , ultimately boosting mitochondrial biogenesis and improving exercise performance(12). In a study, Suwa *et al.* (2008) examined the effect of acute and prolonged endurance training. They reported that acute endurance training resulted in an increase in mRNA-PGC-1 α , but did not change the expression of SIRT1. Also, due to long-term endurance training with high and low intensity, the expression of SIRT1 increases with both severities, but PGC1 α expression increased only during high intensity exercise (13). There are few studies on the effect of physical activity and exercise on the signaling pathway of the transformation of white to brown tissue, so that researchers have not yet been able to improve health-compatibility related to the relationship between the type, intensity and volume of exercises with changes in the fatty tissue phenotype Reach consensus. What is effective and important is that the intensity and duration of exercise should be recognized according to the training program. Although the results of recent studies indicate that increased Irisin hormone level is due to sporty exercises, but it is still associated with signs of a decrease in metabolic syndrome and insulin resistance (14). There are controversial issues about the effect of exercise training on the process of transforming white to brown adipose tissue and its role in the prevention and treatment of obesity. If some studies have reported a significant relationship, and some others have reported an unreasonable relationship between understudy variables by physical activity and practice, it may be due to differences in the methodology of research. However, confirming the assumption that irisin, FNDC5 and UCP1 gene of brown fat tissue are one of

the factors that can activate brown adipose tissue and have anti-obesity effects; in hormonal and metabolic studies, there are still a lot of questions about how irisin level changes through various physical exercises as one of the factors affecting energy balance. The purpose of this study was to evaluate the effect of exercise on effective signaling pathways on stimulating brown adipose tissue in order to increase the consumption of energy and coping with obesity and its complications and turning it into white adipose tissue. In this research various databases such as Google Scholar, SID and PubMed, Science Direct and Scopus have been involved. All the articles chosen in this review were collected from 1998 to 2017. The search keywords contained Training, Exercise, Physical activity, Adipose tissue, Mayokin, PGC-1 α , FNDC5, Irisin, UCP-1. Then, the full manuscripts of the articles and their methodologies were carefully examined. In case of any errors in the study methodology, the article was removed from our analysis. Shorthand form was designed to extract information, which consisted of information about subject, title, journal name, and author.

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha

The PGC-1 α protein encoded by the PPARGC1A gene is a transcriptional activator and acts as an activator of PPAR γ , and regulates the expression of the UCP1 gene and the browning in brown fat. Also, in some cases it has been observed that this protein controls mitochondrial biogenesis and oxidative metabolism in many cells. This protein in the skeletal muscle can cause mitochondrial biogenesis, angiogenesis, and changes in the type of muscle fibers. In addition, it is resistant to dystrophy and muscle atrophy (15). It acts as a mediator in many of the biological mechanisms involved in energy metabolism. This activator controls the biogenesis and mitochondrial respiration by UCP1 proteins and the respiratory factors of the nucleus (16).

nanoseconds of FNDC5 protein can increase the UCP1 gene expression by 7-1500 times. UCP1 has the ability to reduce the amount of proton produced by oxidative phosphorylation.(19).

Irisin

Irisin was discovered in 2012 by Bostrom *et al.* Irisin is a kind of protein with a molecular weight of 12 kDa, consisting of 112 amino acids. Since one of the sources of secretion of this hormone is muscle, it is considered as a myokines. Irisin's target tissue is the adipose tissue. Irisin is the product of breakdown, a type of membrane protein called FNDC5, which is found mainly in the muscle tissue of humans and rats, and can then be released into the plasma (5). Irisin's remarkable feature is similarity in the sequence of its amino acids among mammals. It therefore seems to have a high protective effect. Some studies have shown that irisin plays an important role in preventing diseases of the nervous system, such as Alzheimer's (20).

Muscle activity and Irisin

Muscle leads to an increase in calcium ion from the sarcoplasmic network, followed by calcium neuron and calmodulin kinase. These factors interact with the transcription factors of the binding proteins to the cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), nuclear factor of activated T-cells (NFAT), and the Myocyte-specific enhancer factors (MEF) and D produce PGC-1 α in the nucleus (21). On the other hand, the increase in calcium ion with the effect on AMPK activates PGC-1 α and thus the FNDC5 protein is transcribed inside the nucleus. FNDC5 is broken down by proteolysis and released in the form of the irisin hormone in the blood, and after reaching the irisin target cells, UCP1 increases white fat to brown fat (21). The implementation of acute and prolonged physical activity can increase the expression of PGC-1 α gene expression in skeletal and cardiac muscles, increasing FNDC5 and splitting it and producing irisin.

The high levels of irisin in different tissues leads to its physiological effects in improving health and reducing metabolic diseases. Skeletal muscle can be among the available places for expressing irisin, such as heart muscle, adipose tissue, liver, brain, bone, pancreas, kidneys and ovaries at different levels. Physical activity and exercise can also improve cognitive function of the brain. Increasing the expression of FNDC5 gene in various tissues of the central nervous system such as the midbrain, Brain Bridge, cerebellum, and hippocampus can be highly correlated with increased cognitive function due to exercise activities (21).

Uncoupling protein (UCP)

Uncoupled protein is a kind of protein found in the mitochondria membrane of the brown adipose tissue of mice adapted to the cold and is identified as a caustic agent(22). Uncoupled protein is a type of protein that contains 307 amino acids and a molecular weight of 32 kDa and may account for about 10% of the proteins present in the adipose tissue mitochondria (22). This type of protein has a protein family, uncoupled protein 2, 3, 4, and 5. Unbound protein 2 is found mainly in the adipose tissue and non-conjugated protein 3 in skeletal muscle. Recently, there are two other types of uncoupled proteins found in the brain and the unbranched protein 5 expressed in the testicles and the brain (22). Unlike uncoupled protein 1, which is expressed in abundance in the mitochondria of brown adipose tissue, other non-coupled proteins are expressed at relatively small levels in other tissues (23). Uncoupled proteins are family members of the transmitter that includes all the metabolic carriers of the mitochondrial membrane. One of the most important members of this family is the carrier of the ratio of ATP / ADP, phosphate, oxaloglutarate, aspartate and glutamate (23).

The effect of physical activity on uncoupled protein 1

In conducted studies on rodents, the effects of stimulating exercise on brown fat cells have been reported (24, 25). In this context, the implementation of low intensity exercise can have beneficial effects on the metabolic responses in brown fat tissues (24). It has also been shown that exercise activity associated with exposure to cold leads to an increase in the expression of UCP1 in adipose tissue, while exposure to cold alone does not affect the ability of the activity to produce sports the desired heat of the brown fat tissue is shown (24). Xu *et al.* (2011) reported that exercise activity in rats resulted in a doubling of UCP1 expression and the use of Adiposity progenitor cells (APC) tissue in brown adipose tissue as well as increased thrombogenesis visceral fat tissues (26). DE Matteis *et al.* (2012) reported that by performing exercise activity, the incidence of brown fat cells increased in visceral tissues in rats, and UCP1 levels increased by eight times in brown fat tissue in the exercise group than in the group controlling has increased, and as a result of aerobic activity, the browning of the adipose tissue is reduced (27).

SIRT1

A family of proteins (expressed by genes with the same name) that has both mono- ADP-Ribosyl-Transferases deacetylase activity. This protein family consists of seven members of SIRT1-7 in the mammalian cells (28). SIRT1 is known as an essential protein in antioxidant defense and hemostasis control. In fact, SIRT1 plays role in many vital functions, including controlling free radicals production and fat oxidation through structural histones and many transcription factors (29). SIRT1 induces potential metabolic reactions that delay aging with metabolic changes. These mechanisms involve the two following aspects (30): 1) Increasing stress through adjusting pro-apoptosis factors, such as P53 and FOXO and 2) Providing a series of endocrine

responses that might inhibit fat synthesis and insulin secretion by beta-Langerhans cells through regulating key genes associated with metabolism such as PGC-1 α .

Mechanism in SIRT1 enzyme function

Histone changes affect the base structure of chromatin or nucleotide units. Histone changes are associated with both gene activation and gene repression. Changes in the histone sequence directly change the nucleosomes and thus, it is caused to change the status of the chromatin to a compact state or an open state. Therefore, histone changes can determine the alkaline level of chromatin and the degree of activity of the gene in a particular region of the DNA. For example, lysine sequence in the densified histone has a positive charge and thus can absorb the DNA strand or the negative charge. As a result, compact-chromatin is created that is associated with inhibition of duplication. In contrast, Histone Acetylation causes the removal of negative charge and an open chromatin state, thereby activating transcription(31). Researchers believe that reducing glucose and increasing glucagon, catecholamines and glucocorticoids hormones, increasing levels of cyclic adenosine monophosphate (cAMP), intracellular calcium, stimulating adenosine monophosphate-activated protein kinase (AMPK), and increasing the nicotinic amide adenine dinucleotide to NADH due to sports exercises lead to the activation of SIRT1 (32, 33). PGC1 α is also a key regulator of gluconeogenesis and fatty acid oxidation. SIRT1 is activated by deacetylation and regulates the expression of genes involved in cell growth and energy metabolism. On the other hand, SIRT1 plays a role in the production or control of reactive oxygen species (ROS) through FOXO3 and NF-kB pathways. With the excessive increase in reactive oxygen species (ROS), the SIRT1 function decreases and vice versa. SIRT1 can increase the expression of antioxidant enzymes such as CAT in contrast to free radicals by

activating FOXO transcription factors in the nucleus(34).

Conclusion

In conclusion, the findings of the present study indicated that most of the conducted studies suggest that physical exercise can be effective as an adipose tissue activated agent in the prevention and treatment of obesity. In this regard, irisin seems to be influenced by a variety of sports activities and is a significant factor in the conversion of white to brown adipose tissues and can play a role in weight loss and increase the body thermogenesis.

Ethical issues

Not applicable.

Authors' contributions

All authors equally contributed to the writing and revision of this paper.

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