The Effect of Exercise Trainings in the Stimulation of Brown Adipose Tissue and Transformation of White Adipose Tissue to Brite Adipose Tissue: A Review

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Abstract
There are three types of adipose tissue in the human body: white adipose tissue (WAT), brown adipose tissue (BAT) and beige or Brite adipose tissue. In WAT, energy reserves in the form of triglyceride, while in BAT triglyceride molecules lipolyze for thermogenesis through fatty acid oxidation. A protein called uncoupling protein-1 (UCP1) is responsible for non-shivering thermogenesis in BAT. The most important activators of BAT include peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), sympathetic nervous system (SNS), hypothalamic–pituitary–thyroid axis (HPT axis), endothelium, atrial natriuretic peptides, irisin, β-aminoisobutyric acid (BAIBA), Fibroblast growth factor 21 (FGF21) and interleukin-6 (IL6) that generally exert their effects through stimulation of UCP1 expression and activity. Beige adipose are among white adipose and elevation of UCP1 gene expression is the main cause of their production that atrial natriuretic peptides, PGC1α, irisin, FGF21 and BAIBA are the most stimulators of this transformation. The role of exercise in the stimulation of BAT and transformation of WAT to Brite is discussed in this study.

Keywords: Training, Adipose Tissue

Introduction
Fat is mostly stored in the subcutaneous tissue and in the peritoneal cavity, but there are significant amounts of fat in other tissues of the body in obese people, like the liver. In the past, it was thought that the number of fat cells can be increased only in infancy, and the increase in adipose tissue in children leads to obesity due to an increase in the number of fat cells, and the change in the size of the fat cells is less likely to affect their obesity. In contrast, obesity in adults was thought to be due to an increase in the size of fat cells and causes hypertrophic obesity. However, recent studies have shown that new fat cells can evolve from fibroblastic-like cells around fat cells in each period of life, thus, along with an increase in the size of fat cells, they can also be increased in number which can be effective in obesity in adults. An obese person may have four times the amount of fat in a fat cell that is twice as normal person (1, 2). Obesity is a growing global phenomenon that has increased dramatically over the last decade. The international prevalence of overweight and obesity is reported to be 37% in men and 38% in women, which is higher in developing countries. According to reports in 2010, obesity has caused 3400,000 deaths globally (3). Almost half of Europeans are overweight and obese. Obesity has a direct relationship with many diseases, such as insulin resistance, metabolic syndrome, atherosclerosis, hypertension, cancer and type 2 diabetes. International diabetes federation data show that 382 million people have been infected
with diabetes in 2013, reaching 592 million by 2035. Diabetes has caused 5.1 million deaths in 2013, and every 6 seconds someone dies due to diabetes. Obesity and diabetes impose direct and indirect health care costs on the community (4). The prevalence of childhood obesity in the United States and many other industrialized nations is rising rapidly, rising by more than 34% over the past decade. Approximately 64% of adults in the United States are overweight and around 33% of them suffer from obesity (5, 6). Factors affecting overweight and obesity include increased energy intake compared to energy consumption (7), sedentary lifestyle (8), nutritional disorders (9, 10), endocrine disorders, hypothalamic disorders (11) and genetic factors such as mutations in leptin genes and their receptors (12). The complications of obesity include increased risk of disability and mortality due to diseases such as cancer (13), stroke, diabetes (14- 16) hypertension (17); Gallbladder disease (18); and arthritis (19). Decreased energy intake (20), increased physical activity (21), drug therapy (amphetamine, sibutramine, orlistat, etc.) (22), gastric bypass surgery and using band for the stomach surgery (23) are methods for treating and treating obesity. Regular physical exercises increase physical and mental health and happiness of individuals. Physical exercises also prevent the development of many chronic diseases. In addition, exercise is an excellent therapeutic intervention for controlling obesity, cardiovascular disease, type 2 diabetes, mental disorders, osteoporosis, depression, types of cancer, and many other chronic diseases (24-26). The mechanisms for the beneficial effects of exercise in countering chronic diseases are still not fully recognized. The purpose of this study was to evaluate the effect of regular exercise training on stimulating and invoking brown fat (BAT) to increase energy costs and to cope with obesity and its complications, such as type 2 diabetes and cardiovascular disease.

Brown Adipose Tissue (BAT), White Adipose Tissue (WAT) and Brite
White Adipose Tissue (WAT)
There are two types of adipose tissue in mammals: white adipose tissue (WAT) and brown adipose tissue BAT. These two tissues have different roles in the energy metabolism of the body (27). In WAT, energy is stored in the form of triglyceride (TG) and released in the form of free fatty acids (FFA) and glycerol, while BAT is able to dissipate energy in the form of heat by oxidation of glucose and lipid (28). WAT is the most abundant fat in the human body, which is composed mainly of large spherical adipose that are tightly welded and supported by a connective rich tissue in blood vessels. Its color ranges from white to yellow, and there are all parts of the body except the eyelid, testicular sac, genital organs, and earrings. The thickest part of the cytoplasm of the white adipose is around the broad and adjacent nucleus of the cell that contains the endoplasmic granulosa reticulum, ribosomes, golgi and mitochondrial devices. The adipose tissue is divided into holes by the bladder containing vessels and nerves (29). The size of a fat cell is a determining factor for the function of that cell, and larger fat cells generally have a higher metabolic activity (30). There is a strong external framework of connective tissue to maintain the structure of cells and adipose tissue. The skeletal cell of fat is composed of a network composed of collagen 1 and a lattice fiber whose function is to protect the cell from mechanical stresses (31). Another part of WAT is the steroidal vascular unit, which includes multi-functional stem cells, precursor adipocyte cells, fibroblasts, vascular endothelial cells, lymphatic vessels, macrophages, and refined immune cells (32). WAT is nerve-mediated by the sympathetic nervous system, which is associated with arteries and arterioles, indicating the fact that fat tissue activity can be controlled by this device (33). Also, hormonal control of the function of this tissue
is done by insulin, catecholamines, leptin and glucocorticoids (34). In addition to its primary role as a TG energy store, WAT also secretes hormones called adipicins over many other physiological processes such as lipid metabolism, carbohydrates and proteins, angiogenesis, blood pressure control, blood clotting and immunity. The body is also influential (35).

**Brown Adipose Tissue (BAT)**

The reasons of BAT's importance are the ability of the tissue to increase the amount of base metabolism, increasing exothermic due to cold and food intake, increase the clearance of glucose and lipids, improving cholesterol metabolism and increasing bone density (36-38). Brown adipose are thermogenic cells that are regulated by the sympathetic nervous system (SNS) to increase the temperature when the body is exposed to cold (39). Due to the presence of blood vessels and mitochondria and low levels of fat droplets, the BAT color ranges from light pink to dark red. Too much blood vessels to provide adequate nutrients and oxygen and heat dissipation, TG stores are needed to provide fast energy and SNS nerve stimulation for rapid tissue invagination (40). To maintain long-term exothermic, this tissue receives substrate blood flow (glucose and fatty acid). Finally, exothermal occurs through an uncoupled process, which is performed by Uncoupling Protein-1 (UCP1), a protein found in the internal membrane of the mitochondria in the BAT (41). It has long been believed that BAT exists only in infants and is responsible for non-shivering thermogenesis (42); however, when searching for metabolically active tumors by radiologists using the F-FDG) in positron and computerized radiography (PET / CT) (43-45), a series of symmetrical competitive regions were identified with high levels of glucose consumption. These areas were predominantly in the cervical and supraclavicular regions (46, 47). The presence of BAT in adult humans and its metabolic significance for human physiology was first identified in 2007 (48) and eventually was detected in 2009 (49). There is now no doubt that this unique texture exists and is responsible for thermogenesis in adult humans. BAT activity decreases with age and has an inverse correlation with BMI and visceral fat, and its value is lower in men than in women (50), although in some studies, gender differences were not reported (51). BAT is the most important factor of non-shivering thermogenesis, and when mammals are exposed to shivering thermogenesis temperatures (the temperature at which shivering start), they are exposed to cold. In men, women are more likely to be subjected to vibration than women and obese people. More studies are needed to evaluate BAT activity after exposures to people to determine the vibrational thresholds of the subjects.

**Beige Adipose Tissue or Brite**

Recently, other types of cells have been identified in human or rodents which is called brown-in-white (Brite) in the WAT, which are rich in mitochondria and, like BAT, have UCP1 in their inner membrane (52). These cells share common characteristics of BAT and WAT and their development is regulated by various endocrine, paracrine, and otocrine factors. The evolution of these thermogenesis cells in WAT increases in response to chronic exposure to cold or continuous β-adrenergic stimulation, and their activity is beneficial for the treatment of obesity, type 2 diabetes and other metabolic diseases.

**Non-shivering thermogenesis mechanisms in BAT**

Thermogenesis in BAT is carried out by Uncoupling protein-1 (UCP1), which was first discovered in 1978 (53); this protein exists in the membrane of the mitochondria of brown adiposity and is capable of producing heat through a channel to pass the protons from the membrane to the mitochondrial matrix (54). In most cells of the human body, the
The mitochondrial proton slope is used to produce adenosine triphosphate (ATP), which is the main carrier of energy in all metabolic processes of the human body. However, in BAT, the presence of UCP1 facilitates proton irritation of the internal membrane, thereby it is producing heat instead of producing ATP (55) (Figure 1).

**Figure 1. Detachment of mitochondrial respiration from ATP production**

During rest, UCP1 activity is suppressed by ATP. In response to cold or food intake, norepinephrine affects β3 adrenergic receptors, which causes HSL phosphorylation through cAMP and PKA cascades. HSL phosphorylation leads to lipolysis and the production of FFA, which is used as a beta-oxidation substrate and UCP1 in BAT mitochondria (56). Non-shivering thermogenesis in brown adiposity is accomplished by separating mitochondrial respiration from ATP production. The mitochondrial respiration chain for the production of ATP produces a proton slope along the mitochondrial membrane, which during the stimulation of the BAT, the proton melts gradient is used to generate heat instead of ATP. The main protein in this process, which is also effective in the BAT classification, is the UCP1. The presence of FFA is necessary to facilitate the separation of mitochondrial respiration from ATP production by UCP1 in BAT. The precise amount of FFA contribution to UCP activation is unclear, but probably this substance can provide a membrane input for protons in heat production (Figure 2). It uses glucose other than FFA during the thermogenesis of BAT. Glucose is probably needed to maintain the Krebs cycle, ATP production and proton slope, and can also be converted to FFA (57).

**Effect of transcription regulators on the performance regulation and evolution of WAT and BAT**

The distinction between white and brown adipose begins with adipogenesis, a process that results in intracellular fat accumulation. Adipogenesis is controlled by cascading interactions between several transcription factors, such as Peroxisome proliferator-activated receptor (PPARγ), activator 1 of PPARγ alpha (PGC1α), PR domain containing protein 16 (PRDM16), CCAAT (C/EBP) enhancing protein, the protein C2 is the Forkhead box protein (FOXC2) and Protein 1c bound to the Steroid response element-binding protein 1-c (SREBP1c) (58-61). PPARγ is one of the most important factors that belongs to a large family of nuclear receptors and coordinates the use of adipogenic elements during the differentiation of adipose. This receptor is necessary for the adipogenesis of both white and brown cells. Both adult white and brown adipose express high levels of PPARγ (62). PGC1α is a protein involved in mitochondrial biogenesis and aerobic metabolism in many cells, including skeletal muscle and brown fat, which can increase the expression of mitochondrial grape genes (63). Another important protein, PRDM16, plays a pivotal role in regulating the differentiation and evolution of WAT and BAT, and various factors affect it. One of these factors is bone morphogenetic protein 7 (BMP7), which is an essential signal for the evolution of BAT, which exerts its effects by increasing the amount of PRDM16 mRNA in BAT and WAT (65-67), Thiazolidinediones (TZDs), which
are PPARγ agonists, increase the expression of thermogenic genes in fat cells by the effects of PRDM16 (68, 69).

Figure 2. UCP1 protein function in thermogenesis in BAT. Facilitating Proton Passage from UCP1 by Negative FFA or LCFA Assistance (64).

Also, microRNA 133 (MIR133) reduces PRDM16 levels and thus stops the development of fat for you and BAT. The amount of this substance is reduced by exposure to cold (70-72). Brown adipose are found predominantly in brown adipose tissue reservoirs between the anterior and prefrontal regions and develop in the pre-natal stages. Empirical evidence suggests that brown fats between the mitral region and skeletal muscle originate from cells that express Myogenic factor5 (Myf5) (Fig. 3). It has previously been assumed that this gene is almost exclusively expressed in skeletal muscle precursors. Angirole 1 expressing cells in the central dermomotum transform into brown adipose tissue, skeletal muscle and skin (73).

The role of signal pathways in stimulating WAT and BAT

Sympathetic Nervous System (SNS)

The SNS stimulates BAT to generate heat during non-shivering thermogenesis. Sympathetic neuropathy is essential for activating BAT, and the discontinuation of this nerve can stop the function of BAT (74). Possibly, in humans, the response of the temperature-sensitive neurons to thermal activation is set. The insertion of these neurons into the hypothalamus and module becomes sympathetic stimulator for controlling the heating in the BAT by stimulating adrenergic receptors along the membrane of the BAT cells by the sympathetic nerve-releasing norepinephrine (75). The activity of BAT in rodents is related to both adrenergic receptors of α and β. Although the α1A receptor is abundant in BAT, its stimulation maximally results in 10% of total thermogenesis in rodent BAT. The α2 receptor also stops thermogenesis. The β3 receptor is the most important thermogenesis regulator, therefore, primarily stimulating the β3 receptor and then stimulating the α1A receptor can activate the thermogenesis in BAT, the β1 receptor can only affect BAT’s thermal stimulation only when the β3 receptor signaling is impaired (76). When exposed to cold or food intake, the brain stimulates BAT activity through the SNS. The adiposity of mature brown Norepinephrine that is emitted from sympathetic nerves to β3 receptors coupled to G protein, which is a stimulant of adenylate cyclase, this enzyme causes the conversion of ATP to cyclic adenosine monophosphate (cAMP). The cAMP also causes phosphorylation of protein kinase A and then mitogen p38 activator protein (p38MAPK). P38MAPK also activates lipolysis stimulatory enzymes such as HSL and other lipases, in addition to increasing the expression of the UCP1 and PGC1α gene. (77, 78). The increase in FFA caused by this signal cascade activates UCP1 (Figure 1). Norepinephrine also stimulates glucose uptake in brown adipose. SNS stimulant activity is the release of catecholamines (epinephrine and norepinephrine), which is affected by the volume and intensity of exercise (79). Therefore, the stimulation of adrenergic receptors caused by exercise can have two types of acute effects (UCP1 activation and stimulation of lipolysis and glucose) and chronic (transcription of the UCP1 gene, mitochondrial biogenesis, hyperplasia in BAT,
and conversion of WAT to fatty tissue) on BAT (80, 81).

**Hypothalamus -Thyroid Axis**
Temperature variation is felt by the hypothalamic region, which causes compromise responses, including vasco-activity and thermal regulation in BAT via SNS. Many hypothalamic peptides contribute to the control and evolution of BAT's function. The hypothalamus also responds to dynamic metabolic changes and nutrition through adenosine monophosphate-dependent protein kinase (AMPK). Also, inflammation and hypothalamic dysfunction is a potential contributor to the development of obesity through harmful effects on BAT's function (82). Thyroid hormones play a role in long-term regulation of energy balance and, in collaboration with SNS, enhance adrenergic effects in stimulating BAT. In BAT, the upper levels of type 2 iodothyronine deiodinase are expressed, an enzyme that converts thyroxin (T4) to triiodothyronine (T3) and increases the thyroid signal in BAT when exposed to cold. The activity of thyroid hormones in controlling the function of BAT is regulated by the hypothalamus and AMPK activity (83).

**Endothelium function**
Nitric oxide (NO) is mainly synthesized in endothelial cells, which stimulates gonavial cyclase, sensitive to NO. The stimulation of this enzyme will result in the synthesis of cGMP from GTP, which activates protein kinase G. Protein kinase G also increases the expression of the UCP1 gene, the mitogenicity of the biogenesis, and the production of BRITE cells in WAT (84, 85). Phosphatidylinositol 3-kinase type I (PI3K) is another protein that increases blood pressure in BAT (86).
Hormonal control on WAT and BAT activity

Beta Transforming Growth Factors (TGFβ)

One of the important proteins in suppressing the function of BAT is Transforming growth factor (TGFβ), such as myostatin, that reduces the warming up and expression of the UCP1 gene in BAT, and their suppressing signaling increases BAT and improves insulin sensitivity (87).

Atrial Sodium Peptides

Sodium peptides are a group of hormones produced by the heart. Traditionally the uses of sodium peptides include sodium deficiency in natriuresis, diuresis and vascular dilatation, which together with high pressure on the heart wall are countered. Although receptors of sodium peptides are not limited to kidneys and vessels, adipose tissue is also rich in receptors for atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) as well as receptors for cleansing these hormones (Figure 4). Sodium peptides increase cGMP levels for activation of PKG and PKA, which also cause p38MAPK phosphorylation (88). These effects are consistent with sympathetic beta-adrenergic effects (Figure 5). Sodium peptides also induce lipolysis and expression of the UCP1 gene, thermogenesis, and increased mitochondrial biogenesis (89). One-session exercises increase the sodium peptides, which are due to increased heart rate and tensile wall of the atrial mesothelium (90, 91), which ultimately leads to lower blood pressure (92).

There has been little research on the effects of chronic physical exercises on cardiac sodium peptides, and the results are contradictory in this regard (93-96). Clearly, more research is needed in this case (97). In addition, the effects attributed to sodium peptides, along with the effects of classical adrenergic stimulation, are issues that need to be addressed (Figure 5).

Irisin

Another effective hormone on BAT activity is Irisin. The physical activity of the stimulant is the production of PGC1α from skeletal muscle (98), which stimulates the expression of a protein called fibronectin type III domain containing 5 (FNDC5), which is released into the bloodstream after the irisin-like formulation. After binding to membrane receptor in white adipose, Irisin induces the expression of the UCP1 gene, thereby contributing to the conversion of WAT to BRITE adipose, which is associated with an increase in total energy consumption, weight loss and improved insulin sensitivity (99, 100).

In any case, more research is needed about the effect of physical exercises on this peptide, and the results are contradictory (101, 102).

β-aminoisobutyric acid (BAIBA)

In addition to the irisin, the increase in PGC1α due to exercise can also increase β-aminoisobutyric acid (BAIBA), thereby increasing the expression of BAT-associated genes, which ultimately results in weight loss and improved insulin sensitivity. These BAIBA effects are through mechanisms such as increasing PPARα activity (103). The metabolism of aminoisobutyric acids such as leucine, isoleucine, valine and thymine is effective at the levels of BAIBA (104-106).

Interleukin-6 (IL6)

IL6 is a pro-inflammatory and anti-inflammatory cytokine that is secreted by leukocytes, myocytes and adipose and is effective in regulating the growth, differentiation and metabolism of cells in many tissues (108). For example, in WAT, IL6 increases lipolysis, while it develops skeletal muscle glycolysis and insulin sensitivity (109).

Physical increases IL6 to 100-fold, depending on the intensity and volume of the exercise, the type of muscle contraction (introverted or extrinsic), and the amount of muscle damage (110, 111).
This increase can, by increasing the expression of the UCP1 gene, increase the amount of thermogenesis that occurs through phosphorylation of signal transducer and activator of transcription 3 (pSTAT3), which is a molecular change associated with weight loss (112). Regarding the effects of physical exercises on IL6 in association with BAT, research has only been done on animals, and extensive research has to be done on humans.

**Fibroblast growth factor-21 (FGF21)**

FGF21 is a family member of the fibroblast growth factors that is expressed predominantly in hepatocytes, myocytes, thymus, WAT, and BAT (114-116). It acts as an agent of autocrine, paracrine, and endocrine on BAT, which increases the expression of the UCP1 gene and activates the hemorrhage. In WAT, as well as increasing levels of PGC1α, it can increase the production of adipose tissue (117). Physical activities are supposed to increase levels of FGF21, but the results are contradictory in this case (Figure 6) (118-121), thus, further research with regard to the severity, duration, and type of exercise should be conducted.
Prostaglandins
Cyclooxygenase 2 (COX2) is a restriction enzyme in the synthesis of prostaglandin. The activity of COX2 and prostaglandin E2 has been reported in inducing UCP1 expression in white adipose (121). The expression of UCP1 in WAT and not in BAT may depend on the activity of COX, and therefore the enzyme plays a central role in controlling energy balance and obesity (119).

Orexin
By regulating sympathetic processes, Orexin can increase BAT function, thereby helping to increase energy costs and improve fat percentage (121).

Vascular endothelial growth factor (VEGF)
Exposure to cold increases the chains and growth of blood vessels in adipose to facilitate the exchange of oxygen, nutrients and heat. This angiogenic effect is regulated by increasing the production of vascular endothelial growth factor (VEGF) 111). Interestingly, the substance produced by adipose also increases the appetite for brown and BRITE adipose and improves the metabolic profile (120).

Conclusion
Traditionally it was believed that SNS is the main stimulant of the expression of the UCP1 gene and the activation of BAT and transforming WAT to Brite, and subsequently non-shivering thermogenesis, fat loss and improving insulin sensitivity and lipid profile, which can be attributed to obesity and its consequences like diabetes and coronary artery disease (atherosclerosis). However, new researches have shown that there are a number of new factors affecting the activity of WAT
and BAT that can act independently of SNS, such as irisin, cardiac sodium peptides, IL6, FGF21, BAIBA, TGFβ, and Prostaglandins that appear to be responsive to exercise and physical activity. On the other hand, some transcriptional and signaling factors can also be effective in stimulating WAT and BAT, including PGC1α, PPARγ, PRDM16, C / EBP, SREBP1c, and NO. The effects of various types of physical activity and sports, depending on intensity, duration, gender, age, etc., on the response of these factors to stimulate WAT and BAT, and transforming WAT to Brite, is a new issue that needs to be addressed.

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