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Dorema Aucheri and exercise training in enhancing PPARγ/mTOR/PI3K gene expression in muscle tissue of hypothyroid mice: Experimental approaches using a hypothyroid mouse model

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Abstract

Background: Hypothyroidism is typically associated with a decreased basal metabolic rate, reduced energy expenditure, and weight gain. Exercise training and Dorema Aucheri (DA) have been identified as beneficial therapeutic strategies within complementary health approaches. Skeletal muscle metabolism and fiber type are regulated by innervation and soluble factors, such as thyroid hormones. However, the mechanisms between muscle function and hypothyroidism remain unclear.

Methods: Thirty mice were divided into five subgroups: the normal group; hypothyroid mice (HYPO, 8 mg/kg of propylthiouracil administered via intraperitoneal injection for 30 days); hypothyroid mice treated with DA (Gavaged at 0.4 mg/kg for two months, five days per week); hypothyroid mice treated with exercise (75% VO2 max, 45 minutes per session, for two months, five days per week); and hypothyroid mice treated with both DA and exercise. The mRNA expression levels were detected via real-time qPCR.

Results: The data indicated that PPARγ, mTOR, and PI3K levels are reduced in hypothyroidism. DA and exercise enhanced PPARγ, mTOR, and PI3K levels in muscle tissue. Notably, DA and exercise significantly increased the expression levels of PPARγ, mTOR, and PI3K.

Conclusion: Exercise and DA, as alternative and complementary medicine, modified the PPARγ/mTOR/PI3K signaling pathways affected by hypothyroidism in mice.

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Highlights

What is current knowledge?

- Exercise training may ameliorate the PPARγ/mTOR/PI3K signaling pathway
- DA can regulate PPARγ/mTOR/PI3K expression in hypothyroidism.

What is new here?

Exercise training and DA regulated the metabolism and atrophy signaling pathways in the muscle tissue of hypothyroid mice.

Introduction

Thyroid hormones (THs), specifically tri-iodothyronine (T3) and thyroxine (T4), play a vital role in the growth and maturation of the central nervous system, lungs, and skeletal muscle (1,2). Thyroid-stimulating hormone (TSH) promotes the synthesis and release of THs; however, THs adversely regulate TSH through a feedback loop (2). Skeletal muscle metabolism and fiber type are controlled by innervation and soluble factors, such as THs (3). Hypothyroidism is a condition caused by an underactive thyroid gland, resulting in insufficient production of THs essential for regulating metabolism and overall bodily functions. Common symptoms include fatigue, weight gain, cold intolerance, and depression, which can sometimes be subtle and lead to underdiagnosis (4). This condition is particularly prevalent in women and older adults; in the U.S., approximately 4.6% of the adult population is affected, with higher rates observed in women over 60. If left untreated, hypothyroidism can lead to serious complications such as heart disease, infertility, and severe depression, highlighting the significance of awareness, early diagnosis, and effective management strategies (5,6).

Muscle growth, homeostasis, and regeneration require the binding of T3 to thyroid hormone nuclear receptors (7). Studies have shown that the T3 hormone affects skeletal muscle metabolism and neutralizes muscle atrophy (8). A sufficient serum level of THs is essential for skeletal muscle homeostasis, as muscle function is impaired in both hypothyroid and hyperthyroid conditions (9,10). Skeletal muscle is a crucial component of the body, influencing quality of life, health, survival, and metabolic balance (11). It serves as the body's primary protein reservoir and plays a vital role in regulating glucose and lipid homeostasis (12). Consequently, changes in muscle mass, whether growth or loss, can affect general metabolism, movement, eating, and breathing (13). Research has demonstrated that thyroid dysfunction causes muscle atrophy (14-16).

T3 significantly influences skeletal muscle metabolism and helps counteract muscle atrophy through various mechanisms. By binding to nuclear thyroid hormone receptors, T3 regulates gene expression, promoting the production of anabolic proteins while inhibiting catabolic ones (17). It enhances protein synthesis by activating the mTOR pathway, facilitates the conversion of muscle fibers to more metabolically active fast-twitch types, and increases the uptake of glucose and fatty acids for energy (18). Additionally, T3 may reduce myostatin levels, a protein that inhibits muscle growth. Together, these actions contribute to the preservation and growth of muscle, underscoring T3's importance in maintaining skeletal muscle health (12). In conclusion, hypothyroidism is a complex disease characterized by various physiological symptoms that can significantly impair quality of life, including a decrease in physical performance (19).

The essential oil derived from the above-ground sections of Dorema Aucheri (DA) contains a high concentration of flavonoids and terpenoids (20). However, growing evidence indicates that phytochemicals impact THs and antioxidant enzymes (21). Phytochemical products are valuable substances with diverse applications in daily life (22). These natural compounds may serve as complementary and alternative medicines to help prevent and alleviate disease symptoms, aligning with traditional medical practices (23). According to a recent study, the essential oil derived from the aerial parts of DA is rich in flavonoids and terpenoids, which grant it antioxidant, anti-tumor, anti-diabetic, anti-hypercholesterolemic, anti-hyperlipidemic, and anti-inflammatory properties (24).

Additionally, evidence suggests that combining phytochemicals influences THs, sex hormones, and antioxidant enzyme activity. Given the importance of safety and efficacy in herbal medicine, this study evaluates the effectiveness of the phytochemical cocktail through a computational phytochemistry analysis focused on potential cutpoints in disease pathogenesis (25). Mostafavi et al. demonstrated that DA at a dosage of 0.4 mg/kg protected liver function in a mouse model, compared to higher doses of 0.8 mL/kg, 1.6 mL/kg, and 3.2 mL/kg (24).

Physical activity and exercise training have been defined as beneficial therapeutic strategies in complementary health approaches (26,27). Prolonged exercise training can significantly impact bodily performance, metabolism, and hormonal activity (28). Another key player in regulating metabolism is the peroxisome proliferator-activated receptor gamma (PPARγ)/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) axis. Evidence has demonstrated that exercise training modifies thyroid hormone levels and changes the relative expression of PPARγ (29). PPARγ expression is induced by regular exercise training (30). Huh et al. have shown that plasma PPARγ gene expression increases in response to exercise (31). Importantly, there is a positive association between mTOR and PI3K in trained mice (32).

The aim of this study is to evaluate the therapeutic effects of DA and exercise training on thyroid hormone levels and the expression of the PPARγ/mTOR/PI3K signaling pathways in skeletal muscle hypothyroid mice. It seeks to understand

how DA and exercise training may influence the physiological processes regulated by THs and the expression levels of the PPARγ/mTOR/PI3K signaling pathways in skeletal muscle hypothyroid mice.

Methods

Ethical code

This study was conducted and authorized following the laboratory animal protocols approved by the Islamic Azad University Ethics Committee, Khorasgan Branch (IR.IAU.KHUISF.REC.1400.231).

Thirty six-week-old C57BL/6 mice with an approximate weight of 19 ± 2 g were purchased from the Royan Institute. They were maintained in the animal house of the Isfahan (Khorasgan) Branch of Islamic Azad University under controlled environmental conditions (Temperature of 23 ± 4°C, 60% ± 4% humidity, and a 12-hour light/dark cycle). After one week of adaptation, the mice were separated into two groups: the control group (Mice with no treatment) and the hypothyroidism group, which was injected daily with 8 mg/kg of propylthiouracil (PTU) for one month. The sample size of thirty mice (Six mice per group) was estimated using G*POWER software and a literature review.

It should be noted that in this study, the sample replication was considered as biological replicates. Before assigning the mice to groups, they were typically numbered or tagged for identification. Mice were randomly assigned to groups using a computer program or random number tables. Each mouse was assigned to a subgroup based on the chosen randomization method to ensure that every group had a similar baseline of variables, thus enhancing the reliability of the study results. Therefore, the mice were divided into five subgroups (Each group, n = 6): 1. A control group, 2. Mice with hypothyroidism (HYPO), 3. Mice with hypothyroidism treated with DA at a dosage of 0.4 mg/kg (HYPO-DA), 4. Mice with hypothyroidism treated with aerobic exercise (HYPO-AE), and 5. Mice with hypothyroidism treated with both DA and aerobic exercise (HYPO-DA+AE). The research employed minimally invasive techniques for administering treatments and collecting data to reduce trauma and discomfort to the animals. Moreover, anesthetics were used where appropriate to manage pain and distress during procedures, ensuring the animals experienced as little suffering as possible. Furthermore, continuous monitoring of the animals was conducted throughout the study to assess their well-being, allowing for the timely identification and alleviation of any signs of pain or distress.

Experimental induction of hypothyroidism in mice

Based on the literature review, we selected 8 mg/kg of PTU as the optimal dose to induce hypothyroidism in mice (33). In this study, PTU was administered intraperitoneally at 8 mg/kg for 30 days. During the treatment with PTU, several nonspecific clinical signs were noted in the affected mice. Specifically, while inducing hypothyroidism with PTU, we observed reduced skin turgor, a roughened coat, a hunched posture, and/or decreased activity. Notably, this study did not record any morbidity related to the experimental procedures.

Consuming a mixture of Dorema Aucheri

DA was dried in a darkroom and then powdered using an electric mixer, following the hydrodistillation methodology described in earlier investigations to extract bioactive components. In this study, we administered DA at a 0.4 mg/kg dosage for two months and five days (34).

Aerobic exercise protocol

For eight weeks (5 days/week), mice with hypothyroidism underwent aerobic training on a motorized treadmill. The aerobic exercise performed was moderate to high-intensity interval training. Following one week of adaptation, the training protocol's duration, intensity, and repetitions were progressively increased until reaching approximately 75% of the maximum oxygen consumption (VO2 max) at 45 minutes and a 0 slope. The workout regimen was designed to increase in intensity and speed gradually. The rate of increase was set at 3 m/min and 5% of VO2 max. The protocol started at 10 m/min and 20% VO2 max and progressed to 25 m/min and approximately 75% VO2 max (35). The aerobic exercise protocol is indicated in Table 1.

Table 1. The aerobic exercise protocol

Week	Speed (m/min)	Exercise Duration/Session (min)	Exercise Sessions/Week
Adaptation	7-10	10	5
Firs	7, 10, 13, 10, 7	10, 3, 19, 3, 10	5
Second	7, 10, 13, 15, 13, 10, 7	5, 3, 3, 23, 3, 3, 5	5
Third	10, 13, 16, 17, 16, 13, 10	5, 3, 3, 23, 3, 3, 5	5
Fourth	10, 13, 16, 18, 16, 13, 10	5, 3, 3, 23, 3, 3, 5	5
Fifth	10, 13, 16, 19, 16, 13, 10	5, 3, 3, 23, 3, 3, 5	5
Sixth	10, 13, 16, 20, 16, 13, 10	5, 3, 3, 23, 3, 3, 5	5
Seventh	10, 13, 16, 18, 21, 16, 13, 10	5, 3, 3, 3, 20, 3, 3, 5	5
Eighth	10, 13, 16, 19, 22, 16, 13, 10	5, 3, 3, 3, 20, 3, 3, 5	5

Measurement of hormone levels

Blood collection was performed under anesthesia to minimize distress. The operator inserted a needle directly into the heart through the chest wall to collect blood. The serum was then separated using a centrifuge at a speed of 3100 g for 5 minutes at a temperature of 4°C. The concentration levels of T3 (MYBIOSOURCE, MBS262762) were measured to confirm the presence of hypothyroidism.

RNA extraction and qPCR-Real Time

The muscle tissue samples were subjected to RNA extraction using Trizol reagent (Thermo Scientific, USA) according to the manufacturer's instructions. The RNA quality was assessed using NanoDrop spectrophotometry (Thermo Scientific, Waltham, MA, USA). Next, cDNA synthesis was performed according to the manufacturer's protocol provided by TaKaRa. mRNA primers were designed using Oligo 7 and Beacon Designer 7 software. In addition, real-time qPCR was performed using SYBR Green dye (TaKaRa, Kusatsu, Japan) on a Rotor-Gene 6000 apparatus (Corbett Life Science, Mortlake, Australia). The study utilized 18S ribosomal RNA (18S rRNA) as a reference gene to standardize the expression of genes (Table 2).

Table 2. The sequences of primers used for real-time PCR

Genes	Sequences (5'- 3')
PPARγ-f	CTGTTATGGGTGAAACTCTGG
PPARγ-r	GTGGTAAAGGGCTTGATGTC
PI3K-f	ACACCACGGTTTGGACTATGG
PI3K -r	GGCTACAGTAGTGGGCTTGG
mTOR-f	AGAAGGGTCTCCAAGGACGACT
mTOR-r	CTCCAAAGGCACTTGACTGCTG
18S rRNA -f	CGGACACGGACAGGATTG
18S rRNA -r	TCGCTCCACCAACTAAGAAC

Statistical analysis

The analysis of variances was computed using GraphPad Prism Software (Version 9, GraphPad Software Inc., La Jolla, CA). In addition, the Shapiro-Wilk test was employed to assess the normality of the distribution in this study. Furthermore, all data were analyzed using one-way analysis of variance (ANOVA) with Tukey's post hoc test and t-test. The results are presented as the mean value ± standard deviation (SD). Differences with a P-Value < 0.05 are considered statistically significant in all analyses.

Results

The T3 hormone changed by exercise training and Dorema Aucheri

The concentration of T3 hormone in hypothyroid mice was significantly different compared to the control group (Table 3, P-Value < 0.001). Based on the data, T3 concentration was reduced in the HYPO group compared to the Control group (Table 3, P-Value < 0.001). In addition, it was observed that the concentration of T3 in the HYPO-DA and HYPO-AE groups was higher compared to the HYPO group (Table 3, P-Value < 0.001). Furthermore, the concentration of T3 significantly increased in the HYPO-DA+AE group compared to the other groups (Table 3, P-Value < 0.001).

Table 3. The T3 concentration

Groups	T3 concentration (ng/ml)	P-Value
Control	7.31±0.64	0.001 < P
HYPO	1.2±0.16[a]	0.001< P
HYPO-DA	3.64±0.65 [ab]	0.001 < P
HYPO-AE	3.12±0.39 [ab]	0.001< P
HYPO-DA+AE	5.64±0.98 [abcd]	0.001< P

All data are presented as mean ± SD. "a" indicates the significance between the normal and other groups. "b" indicates the significance between the HYPO and other groups. "c" indicates the significance between HYPO-DA and HYPO-DA+AE. "d" indicates the significance between HYPO-AE and HYPO-DA+AE.

The expression level of the PPARγ/mTOR/PI3K enhanced by exercise training and Dorema Aucheri

The PPARγ/mTOR/PI3K expression level in the HYPO group significantly decreased compared with the control group (Figure 1a-c, P-Value < 0.001). Our data showed that DA increased PPARγ gene expression in the muscle by 0.16-fold (Figure 1a, P-Value < 0.001). Moreover, exercise training enhanced PPARγ gene expression in the muscle by 0.25-fold (Figure 1a, P-Value < 0.001). It should be noted that the relative expression of PPARγ was amplified in the muscle of the HYPO-DA+AE group by 0.46-fold (Figure 1a, P-Value < 0.001).

PTU reduced the relative expression of mTOR in the muscle of HYPO mice by 0.42-fold (Figure 1a, P-Value < 0.001). The mTOR expression level was significantly increased by DA (0.1-fold) and aerobic exercise (0.19-fold) (Figure 1b, P-Value < 0.001). In addition, the mTOR gene was elevated in the muscle of the HYPO-DA+AE group by 0.41-fold (Figure 1b, P-Value < 0.001).

The PI3K expression level in the muscle of HYPO mice was reduced by 0.46-fold (Figure 1c, P-Value < 0.001). The PI3K gene was significantly amplified by DA (0.11-fold) and aerobic exercise (0.16-fold) (Figure 1c, P-Value < 0.001). Furthermore, the PI3K gene was raised in the muscle of the HYPO-DA+AE group by 0.3-fold (Figure 1c, P-Value < 0.001). Notably, we found that the relative expression of PPARγ/mTOR/PI3K was improved in the HYPO-DA+AE group (Figure 1a-c, P-Value < 0.001).

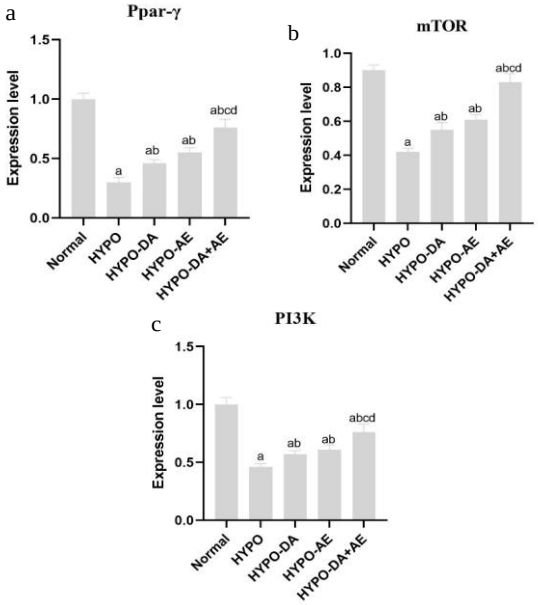

Figure 1. The Dorema Aucheri and exercise training regulated PPARγ/mTOR/PI3K pathway. a. the relative expression level of PPARγ. b: the relative expression level of mTOR. c: the relative expression level of PI3K. All data are shown as mean ± SD. a indicates the significance between the normal and other groups. b indicates the significance between the HYPO and other groups. c indicates the significance between HYPO-DA and HYPO-DA+AE. d indicates the significance between HYPO-AE and HYPO-DA+AE.

Discussion

The present study showed that hypothyroidism in mice impaired the PPARγ/mTOR/PI3K pathway. Our results showed that the PPARγ/mTOR/PI3K expression level significantly decreased in hypothyroidism in mice. Moreover, we demonstrated that the PPARγ/mTOR/PI3K pathway was dysregulated. Furthermore, we revealed that the expression level of PPARγ/mTOR/PI3K was reversed by exercise training and DA.

Skeletal muscles are one of the important components of the body that are related to quality of life, health, survival, and metabolic balance (11). Skeletal muscle is the protein reservoir of our body and an essential regulator of glucose and lipid homeostasis (11,36). As a result, the growth or loss of muscle mass can affect general metabolism, movement, eating, and breathing (13). Therefore, it is not surprising that excessive muscle loss is a poor prognostic indicator for a variety of diseases, including cancer, organ failure, infections, and unhealthy aging (37). Muscle function is influenced by different qualitative systems that regulate the function of proteins and contractile organelles (38). It is worth mentioning that the expression of genes in skeletal muscle can depend on THs. MCT8 and MCT10, thyroid hormone transporters, and thyroid hormone converting enzymes, DIO2 and DIO3, are expressed in the skeletal muscle of humans and rodents (39).

We found that consuming DA could improve the PPARγ/mTOR/PI3K expression level in hypothyroid mice. DA contains calcium and magnesium, which can produce and increase TSH as a mediator of the second messenger through the calcium-phosphatidyl-inositol mechanism (40). In addition, coumarin is one of the compounds in DA that affects thyroid function by inhibiting the conversion of T4 to T3 (41). It also contains many antioxidant agents, such as flavonoids, anthocyanins, and phenolic acid (42).

Our data indicated that the expression level of mTOR changed in the hyperthyroid condition. Coppola et al. established that in a rat model with central hyperthyroidism, the activation of the mammalian target of rapamycin (mTOR) signaling in the arcuate nucleus (ARC) of the hypothalamus enhanced feeding (43). Additionally, Coppola et al. demonstrated that fasting stimulates the local production of T3 in the ARC, which promotes feeding by increasing UCP2-mediated mitochondrial uncoupling (43). It can be deduced that the converse happens in hypothyroidism, as Coppola et al. have documented reduced levels of hypothalamic Ucp2 mRNA under hypothyroid conditions. Moreover, there is a correlation between heightened SNS signaling and lower food intake (44,45). Evidence has demonstrated that mTOR signals in the central circadian clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, control the production of clock proteins Period 1 and Period 2, thereby modifying circadian rhythms. As previously stated, THs control mTOR signaling in the ARC to enhance food intake; thus, it is reasonable to assume that hypothyroidism affects mTOR signaling in the suprachiasmatic nucleus (SCN) (46). Nevertheless, a comprehensive investigation is still required to determine the mechanisms by which TH diseases induce metabolic and behavioral alterations by modifying circadian rhythms (47).

DA, a traditional herbal plant, has gained attention for its potential effects on thyroid function (24). It has been noted for its ability to modulate thyroid activity, which may be beneficial in both hyperthyroidism and hypothyroidism by supporting the regulation of THs (24). Calcium ions are crucial in numerous cellular processes, including hormone secretion. Phosphatidylinositol (PI) is a phospholipid in cell membranes that can be phosphorylated to generate inositol trisphosphate (IP3). This process is essential for mobilizing intracellular calcium. Increased intracellular calcium levels can promote the secretion of THs by stimulating the exocytosis of thyroid follicle cells. Enhanced calcium signaling can increase the synthesis and release of THs (T3 and T4), improving metabolic functions and energy regulation. Coumarins are a class of compounds found in various plants, including DA (48). They possess anti-inflammatory, antioxidant, and potential endocrine-modulating properties. Some studies suggest that coumarin compounds may influence thyroid function by interacting with thyroid hormone receptors or pathways involved in their synthesis. Improvements in PPARγ/mTOR/PI3K expression could signify that DA facilitates favorable environments for thyroid hormone synthesis and secretion through enhanced energy metabolism and cellular signaling pathways. The modulation of calcium levels via phosphatidylinositol and the influence of coumarins may support these pathways, improving thyroid health and function.

In this study, we found that the relative expression of PPARγ/PI3K was improved by exercise training. Exercise can regulate the amount of hormones secreted by the thyroid gland. Furthermore, since exercise regulates metabolism in muscle tissue over the long term, it can have a dual effect on the function of the thyroid gland and the locomotor system. By increasing THs, exercise regulates both bone metabolism and muscle function, thereby improving hypothyroidism. Implementing specific exercise protocols can affect the regulation of thyroid hormone levels over the long term and positively improve the function of other body tissues, including bone and muscle (49). It is well-known that exercise affects the activity of many glands and their hormone production (49), and increasing blood circulation leads to improved thyroid hormone production and body metabolism (50). On the other hand, exercise also leads to the secretion of epinephrine, cortisol, growth hormone, prolactin, and other factors that modulate the immune system (51).

Conclusion

It seems that the use of medicinal plants, along with exercise training, can have a better protective effect on hypothyroidism in mice. According to the results of the present study, DA and aerobic exercise modified the PPARγ/mTOR/PI3K signaling pathways induced by hypothyroidism in mice.

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Ethical statement

All animal studies were performed following the standard ethical guidelines for working with laboratory animals, approved by the Azad University of Isfahan (Khorasgan, Iran), and after receiving the code of ethics (IR.IAU.KHUISF.REC.1400.231).

Conflicts of interest

The authors declare that they have no conflict of interest.

Author contributions

MB: carried out the experiments and drafted the manuscript. FT: participated in this study as the supervisor and contributed to the study design, conceptualization, data analysis, validation, and manuscript revision. KHJD and RM: participated in data validation and manuscript revision. All authors read and approved the final manuscript.

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