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The effects of whey protein-based beverage formulation on the expression of genes related to lipid metabolisms, muscle function, and oxidative stress in trained mice

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Abstract

BACKGROUND: The expression of metabolic genes can be changed by the simultaneous effect of endurance exercise and nutrition. The aim of this study was to verify the effects of endurance exercise and whey protein consumption on the expression of Fibronectin type III domain-containing protein 5 (*FNDC5*), Paraoxonase-1 (*PON1*), and proliferator-activated receptor alpha (*PPARα*) genes in muscle.

METHODS: A total of twenty BalB/C male mice were accidentally selected and subsequently divided into four groups, with each group consisting of five mice. The groups were as follows: placebo, exercised, whey-supplemented, and exercise plus whey-supplemented. In the groups involving exercise, the animals underwent treadmill exercise three times per week. The expression of *FNDC5*, *PON1*, and *PPARα* genes was analyzed by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Finally, GraphPad Prism 9.0 software was used to statistically evaluate changes in gene expression, and one-way analysis of variance (ANOVA) at the $p<0.05$ level and Tukey's multiple comparison test.

RESULTS: *FNDC5* gene expression in muscle increased in the groups that were supplemented with whey or exercised, compared to the placebo group. Investigations did not show a significant difference in *FNDC5* expression in the liver between the whey-supplemented, exercise plus whey-supplemented, and placebo groups. In both liver and muscle tissue, whey protein increased the expression of PON1 ($P = 0.001$) regardless of exercise. *PPARα* expression also increased in muscle tissue. Additionally, the expression of *PON1* in muscle was higher in the whey-supplemented group compared to the exercise and placebo groups.

CONCLUSION: The consumption of whey protein and its interaction with exercise can significantly contribute to the modification of energy and lipid metabolism, muscle function, and oxidative stress through increased metabolic gene transcription.

Keywords: Metabolic Gene Expression; Whey Protein; Exercise; Gene Expression; Muscle Function

Introduction

Milk protein is a highly valued nutritional source due to its superior quality and completeness in terms of essential amino acids. During the cheese-making process, milk undergoes curdling, which leads to the separation of whey protein from the milk. The extracted whey protein can be utilized for various applications in the food and beverage industries, such as functional ingredients, dietary supplements, and athletes' food products. Because of its high nutritional valence, versatility, and functional components, whey protein and its derived products are popular food supplements among consumers and food manufacturers[1]. Whey protein is a byproduct of curds formation, which is obtained through direct acidification of milk. This byproduct is a complex mixture of proteins that includes glycomacropeptide (GMP), bovine serum albumin (BSA), α-lactalbumin, β-lactoglobulin, immunoglobulins, and several other minor proteins[2].

Whey proteins have demonstrated suitability for incorporation into athletes' drinks, as they contain a variety of amino acids that may serve as a source of energy and protein supply, thereby facilitating muscle growth. Recent research and development initiatives have emphasized the potential of whey proteins in regulating blood glucose levels and enhancing feelings of satiety, which may be of particular interest to individuals seeking to improve their metabolic health[3]. Also, whey proteins can help rehydration after exercising[4]. Consuming a diet rich in protein can be beneficial in terms of promoting the loss of body fat, while also enhancing the sensation of satiety, which is a crucial aspect of maintaining an optimal body weight. A positive solidarity has been shown between higher protein diets and increased thermogenesis. A higher thermogenic effect can increase the body's ability to burn calories and promote weight loss[5]. Studies have also indicated that whey proteins can encourage bone formation and stimulate bone cells[6]. Whey proteins are also recognized for their excellent emulsifying and stabilizing properties, which make them an ideal option for producing stable beverage formulations[7].

Numerous scientific studies have indicated that an individual's diet and exercise regime can substantially influence the expression of various genes[8-10]. Previous studies showed that prolonged intake of whey protein or amino acids can upregulate diverse gene expressions in skeletal muscle tissue, resulting in a marked increase in muscle filaments and strength[11-13]. During physical training, the process of muscle fiber biosynthesis is disturbed. However, within the initial hour of exercise completion, the process of muscle protein synthesis is augmented and can persist for 24 to 48 hours. Studies have shown that consuming meals high in protein after exercising can stimulate protein synthesis in the skeletal muscles. Therefore, using protein-based nutrition, specifically whey protein, is a practical approach to control metabolic pathways after a workout[14-16].

Paraoxonase-1 (PON1) is a glycoprotein belonging to the paraoxonases family. It exhibits potent antioxidant properties as well as anti-inflammatory effects. The primary site of PON1 expression is the liver, and upon secretion into the blood revolve, it binds to high-density lipoproteins (HDLs). The association of PON1 with HDLs is attributed to the ability of PON1 to protect against oxidative damage to lipoproteins, thereby reducing the risk of cardiovascular disease. PON1 exhibits other physiological functions, including detoxification of organophosphorus compounds and inhibition of bacterial infections[17]. The compound under investigation was initially discovered for its ability to hydrolyze paraoxon. However, subsequent research has revealed its potential as an antiatherogenic agent[18]. PON1 has a protective role against some disorders related to inflammation and oxidative stress, including non-alcoholic fatty liver disease and different types of diabetes[19].

Fibronectin type III domain-containing protein 5 (FNDC5) is present in various tissues, including liver, fat, heart, and kidney, and is expressed in skeletal muscle. FNDC5 expression in muscle gamma 1 alpha receptors is increased by peroxisome proliferator (PGC-1alpha), which is compatible with exercise. Expression of

FNDC5 induces the generation of a new protein called irisin in mice[20,21]. Peroxisome proliferator-activated receptor alpha (PPARα) controls lipid metabolism by regulating gene expression of some enzymes associated with energy generation[22]. For example, gene expression of two major enzymes related to triglyceride degradation, namely hormone-sensitive lipase (HSL) and lipoprotein lipase (LPL), was increased by PPARα[23].

In this study, the effect of whey beverage consumption was investigated on enhancing the health benefits of exercise, based on the changes in the expression of FNDC5 and PON1 genes in the muscle and liver tissues, and PPARα genes in the muscle tissue of mice.

Materials and Methods

The whey protein concentrate (WPC) was obtained from German Prot (Germany) with ingredients of approximately 81.4% protein, 3.75% ash, 6.06% lactose, and 6.02% fat.

Preparation of whey-based beverage

The whey protein concentrate was mixed with gum and the resulting mixture. Then the mixture was homogenized using an IKA homogenizer (Package DI 18™ and DI 25™ yelloline) at 8000 rpm/min for 5 minutes and then was mixed with sugar and distilled water on a stirrer at a speed of 5000 rpm for 10 minutes. Afterward, the mixed beverage was heated at 75°C for 5 minutes, cooled to 20°C, and then stored in polyethylene terephthalate (PET) containers at 4°C for 28 days. The beverage contained 12% WPC and 6% sucrose in the formulation.

Animals and experimental design

Male BalB/C mice (20) with four weeks old were from Royan Institute (Isfahan, Iran). The mice were kept in a room at 24 ± 3°C and 65% humidity at a 12:12 light-dark cycle. At six weeks of age (18 ± 2 g), the mice were partitioned into four groups randomly, with five mice in each group. The categories consisted of 6% sugar solution dietary (placebo), regular diet with concurrent exercise training (exercise group), supplemented with 300 mg/kg/day of the whey beverage without exercise training (supplemented group), and supplemented with 300 mg/kg/day whey beverage with simultaneous exercise training (exercise-supplemented group). The standard food (4.5% (w/w) fat, 23% (w/w) protein, and 4.5% (w/w) fiber) and tap water were made available to the mice with no restrictions.

Exercise training

For eight weeks, exercise was performed at a moderate to high intensity on a treadmill for three days every week. The running speed and exercise period were gradually increased (70% VO_2 max, 25 m/min for 20 min).

Sampling and laboratory measurements

Xylazine (10 mg/kg) and ketamine (80 mg/kg) were used to kill the mice after 7 hours of fasting, and then their liver and gastrocnemius were removed. The tissues were then immediately cooled with physiological serum, cleaned, and placed inside a microtube, and kept at -70°C until the measurements' performance.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

RNA was extracted from the gastrocnemius muscle and liver of mice using TRIzol reagent (Sigma, USA). For this purpose, first tissue samples were homogenized in TRI Reagent (1 ml for 50-100 mg of tissue) in a Polytron homogenizer (Fisher Scientific). Then the samples were allowed to stand for 5 minutes at room temperature, and 1 ml TRIzol reagent and 0.2 ml of chloroform were added to it. Following a shake for 15 seconds and standing for 2-15 minutes, centrifugation was done at 12,000 × g for 15 minutes at 2-8°C. Then, the colorless upper aqueous phase (containing RNA) was separated, and 0.5 ml 2-propanol was added to it and mixed. The sample was allowed to stand for 5-10 minutes at room temperature and then was centrifuged at 12,000 × g for 10 minutes at 2-8°C. The supernatant was removed, and the RNA pellet was washed using 1 ml of 75% ethanol and then centrifuged at 7,500 × g for 5 minutes at 2-8°C and dissolved in 50 µl RNase-free water.

A volume of 2 µl DNase I (10 U, TaKaRa) was used to remove genomic DNA contamination from 50 µg of the extracted RNA in a mixture containing 10 µl DNase I buffer (10X) and 20 U of ribonuclease inhibitor, in a total volume of 50 µl, which was adjusted using RNase-free water. The manufacturer's instructions for cDNA synthesis using a cDNA synthesis kit (TaKaRa) were to use 1 µg of RNA in a mixture containing 1 µl random hexamer primer (50 µM) and 1 µl dNTP mix (10 mM each), in a total volume of 10 µl, which was adjusted using RNase-free water. QRT-PCR was performed using SYBR Green (TaKaRa) in a Corbett Rotor-Gene 6000 (Qiagen) thermocycler. Expression of FNDC5, PON1, and PPARα genes of muscle, and FNDC5 and PON1 genes of liver tissues, was assessed by matching to the ΔΔCT pattern. The sequences of the primers purchased from Micro- Gene Co., in South Korea.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism software (version 8.0, GraphPad Software Inc., La Jolla, CA). Results were presented as mean ± standard error of the mean (SEM). Differences between study groups were assessed using nonparametric tests (Kruskal-Wallis test for more than two groups, and Mann-Whitney U test for two groups). Significant differences were considered at the $p<0.05$ level.

Ethics approval

The ethics committee of the Islamic Azad University of Falavarjan (IR.IAU.FALA.REC.1402.048) has granted permission to conduct experiments on mice.

Results

The expression of FNDC5, PON1, and PPARα genes in muscle, and FNDC5 and PON1 in liver tissues, was assessed. Results indicated that whey supplementation increased the expression of FNDC5 and PON1 genes in both muscle and liver, and the expression of the PPARα gene in muscle (Figs. 1 to 3). Whey-supplemented and exercise plus whey-supplemented groups increased the expression of muscle FNDC5 genes in comparison

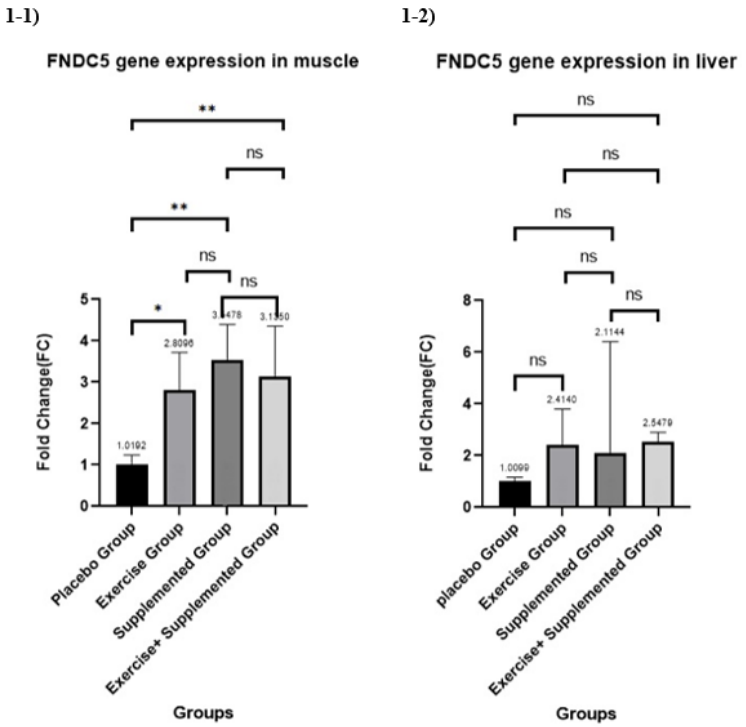

Fig. 1. *FNDC5* gene expression Changes between different experimental groups of mice: 1-1) *FNDC5* gene expression in muscle tissue (P.= 0.001); 1-2) *FNDC5* gene expression in liver tissue (P= 0.7). ns: nonsignificant ($p > 0.05$); *: $p < 0.05$; **: $p < 0.001$.

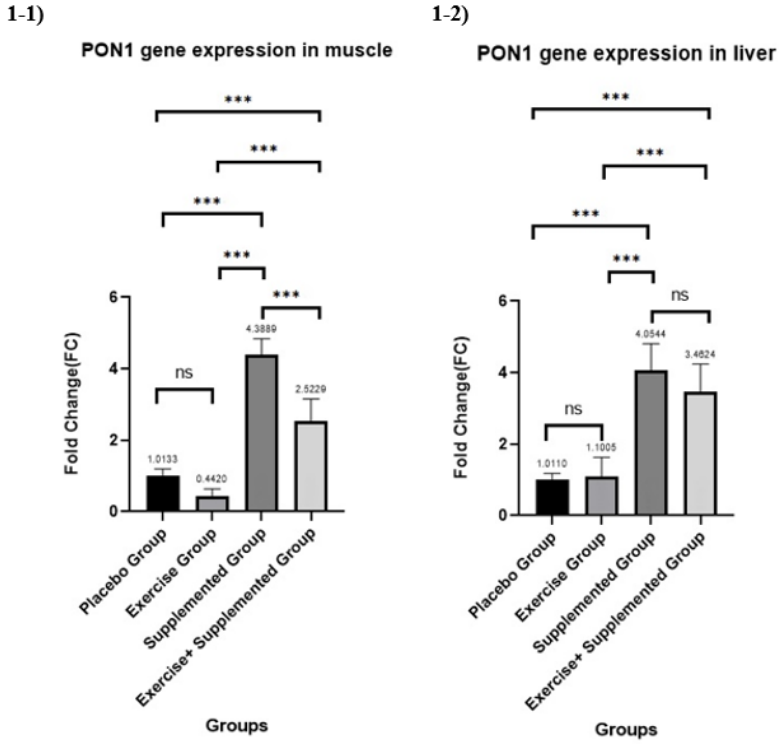

Fig. 2. *PON1* gene expression Changes between different experimental groups of mice: 1-1) *PON1* gene expression in muscle tissue (P= 0.0001); 1-2) *PON1* gene expression in liver tissue (P= 0.0001). ns: nonsignificant (p > 0.05); ***: p < 0.0001.

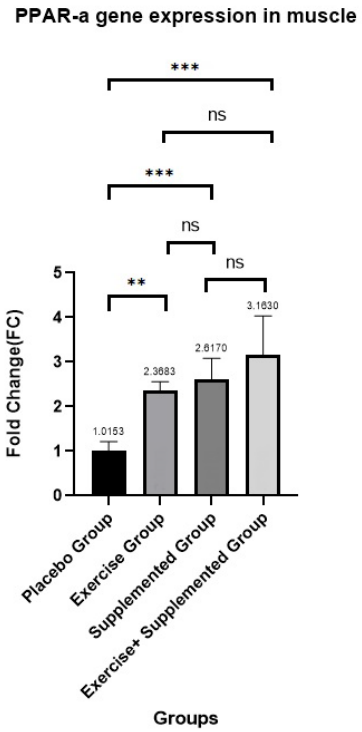

Fig. 3. *PPAR* gene expression Changes between different experimental groups of mice: *PPAR-α* gene expression in muscle tissue (P= 0.0001). ns: nonsignificant (p > 0.05); **: p < 0.001 and ***: p < 0.0001.

with the placebo group (p<0.05) (Fig. 1-1). There was no significant difference in FNDC5 expression between the whey-supplemented, exercise plus whey-supplemented, and placebo groups in the liver (Fig. 1-2).

The expression of *PON1* genes increased in both muscle and liver after whey supplementation. As expected, whey-supplemented and exercise plus whey-supplemented increased the expression of *PON1* in both experimented tissues compared with the placebo and exercise groups (p < 0.0001) (Fig. 2). The *PON1* expression increased in the whey-supplemented group more than in the exercise group (Fig. 2).

Exercise increased expression levels of *PPAR* (Fig. 3) in comparison with the placebo group p<0.05. In contrast, the maximal increase in *PPAR* yielded when whey supplemented (Fig. 3). However, whey-supplemented and exercise plus whey-supplemented increased the amount of PPARα in the muscle tissues in comparison with the placebo (p < 0.001) (Fig. 3).

Discussion

Our findings suggest that the use of whey supplement modifies the expression of various metabolic pathways and oxidative stress regulating genes, including FNDC5 and PON1 in the liver and gastrocnemius muscle, and the PPARα gene in muscle. The importance of exercise in increasing gene expression has been documented previously[24]. In addition, different compounds found in foods can impact metabolic processes, the expression of genes, and the creation of proteins. Previous studies have shown that consumption of whey supplements can stimulate the activation of various genes dependent on protein synthesis and also hinder protein breakdown through the mTOR pathway, which leads to an increase in muscle mass[25].

We have found that adding whey supplements resulted in higher transcript levels of the FNDC5 gene in the muscle. These findings confirmed the previously established concepts related to this topic. The synthesis of irisin, a myokine that has been recently discovered and is involved in regulating energy metabolism, can result from the presence of FNDC5 in muscle[26]. Irisin production is a metabolic pathway resulting from the proteolytic degradation of FNDC5 protein and is secreted as a sports hormone during exercise and with whey supplement use in skeletal muscles[27]. According to in vitro and animal studies, there is evidence that FNDC5/irisin can induce a brown fat-like phenotype[28]. Animal models subjected to overexpression of the Fndc5 gene displayed a considerable increase in the upregulation of UCP1 and several mitochondrial genes, leading to an increase in oxygen consumption. The results of experiments have shown that glucose tolerance ameliorated and insulinemia reduced, suggesting an improved metabolic profile due to elevated energy expenditure[29].

Whey protein, which is rich in leucine, reportedly improves protein synthesis through the PI3K–AKT pathway and inhibits proteolysis by reducing the expression of atrogin-1/MAFbx and MuRF1, responsible for muscle homeostasis through the activity of the AKT/mTOR signaling pathway. The signaling required for mRNA translation initiation, a key regulatory site in cellular protein synthesis, is mediated by mTOR[30]. It was observed that muscle Fndc5 was upregulated by whey protein, indicating that the regulatory mechanisms between the liver and gastrocnemius muscle of mice fed with whey protein may differ. Previous studies have shown that mTOR levels increased in the gastrocnemius muscle of mice fed with whey protein for seven consecutive days[31,32]. Whey protein not only increases protein synthesis by modulating the IGF-1–PI3K/AKT/mTOR signaling pathway, but also improves protein degradation by regulating UPP and ALP via FOXO-mediated transcription of critical genes, resulting in beneficial effects on muscle protein homeostasis[33].

Our data revealed that the interplay between exercise and whey supplementation had a synergistic effect on the induction of PON1 transcription. PON1 is encoded by a multigene family and is produced in the liver. PON1, PON2, and PON3 show extensive structural homology and are located adjacently on chromosome 7[34]. PON1 as an enzyme can be relevant to HDL, LCAT, and platelet-activating factor acetyl-hydrolase. The antioxidant effects of HDL are activated by these enzymes[35].

The observations in the present study indicate that the levels of PPARα expression increased in muscles of mice subjected to exercise supplemented with whey. These findings could have significant implications for the development of new food formulations, promotion of metabolic health, and improvement of exercise performance. PPAR is a type of nuclear transcription factor that has an important role in adipogenesis and fat deposition regulation. According to current research, physical activity may enhance the potential of skeletal muscles to carry out aerobic metabolism. This is thought to occur through the amplification of mitochondrial capacity, which enables the production of ATP via oxidative phosphorylation. It is believed that this upregulation in PPAR expression may be responsible for this effect. The results of other studies have shown important concepts for proving the beneficial mechanisms behind exercise, healthy eating, and fitness[36].

Moreover, the incorporating of whey protein into diet has shown to provide numerous benefits, including the potential to increase the size of muscle fibers and enhance physical endurance. Additionally, whey protein has been found to promote the activity of mitochondrion, which is responsible for the energy production within cells. Furthermore, the consumption of whey protein supplements causes a reduction in reactive oxygen species (ROS) in the body, thereby serving as an antioxidant in the protection against harmful free radicals[37].

PPARs are responsible for regulating the degradation of triglycerides through certain transcription factors, along with the enzymes HSL and LPL. The gastrocnemius muscle was found to have an increased transcriptional upregulation of PPARα due to whey protein intake[38]. The observed upregulation of LPL gene expression in the gastrocnemius muscle indicates an enhancement in the supply of fatty acids through the breakdown of triglycerides. This finding suggests an increased potential for lipid metabolism and utilization in the muscle tissue. Such upregulation may be significant for the regulation of cellular energy balance and substrate utilization in the context of metabolic disorders and physical activity. These results provide a new approach to molecular pathways affecting lipid metabolism in the muscle tissue, which may provide researchers and clinicians new treatment methods[39].

The expression of apolipoprotein A1, the primary apoprotein found in HDL, and ATP binding cassette A1 (ABCA1) increases with PPARα activation, a complex that facilitates the transportation of cholesterol efflux from cells[40]. The promoter region of the PON1 gene is known to contain several putative PPARα binding sites. Activation of PPARα leads to an increase in the expression of PON1. Regulation and coordination of PON1 and MCP-1 expression is pertained to PPAR[41].

Conclusion

Our investigations indicate that consumption of whey protein beverage during exercise has a great potential to change the expression level of FNDC5, PON1, and PPARα genes in the gastrocnemius muscle. Nonetheless, further research is required to confirm the physiological implications of these findings.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: HN; AMA
Data Acquisition: AA; AMA; ABM
Data Analysis or Interpretation: HN; AA; AMA
Manuscript Drafting: HN; AA
Critical Manuscript Revision: HN
All authors have approved the final manuscript and are responsible for all aspects of the work.

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