Orginal Article
Open Access
Iranian Journal of Diabetes and Obesity (IJDO)

The Effect of 8 Weeks of Swimming Training Combined with Berberine Supplementation on Mitochondrial-Derived Peptides (MOTS-c and Humanin) in the Liver Tissue of Obese Diabetic Rats

Sirous Farsi*
Department of Sports Physiology, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran.

Abstract

Objective: Type 2 diabetes and obesity are associated with mitochondrial dysfunction and reduced levels of mitochondrial-derived peptides such as MOTS-c and Humanin. This study investigated the combined effect of swimming training and berberine supplementation on the levels of these peptides in the liver tissue of obese diabetic rats.

Materials and Methods: 30 male Wistar rats were randomly assigned to 5 groups: Healthy Control (HC), Obese Diabetic (OD), Swimming Training (ODST), Berberine (ODB) and Swimming Training + Berberine (ODST+ODB). Diabetes was induced by a high-fat diet and streptozotocin injection. The swimming protocol lasted 8 weeks and berberine was administered at a dose of 150 mg/kg. Protein levels of MOTS-c and Humanin were measured by ELISA.

Results: Diabetes and obesity induction significantly decreased MOTS-c and Humanin levels in the OD group compared to HC ($P< 0.001$). Swimming or berberine alone did not significantly increase peptide levels (MOTS-c: $P= 0.604$ and P=0.748; Humanin: $P= 0.13$ and $P= 0.12$, respectively). However, the combined intervention (ODST+ODB) significantly increased MOTS-c ($P= 0.003$) and Humanin ($P= 0.02$) compared to the OD group. Humanin levels in the combined group returned to HC levels ($P= 0.08$), whereas MOTS-c remained lower than HC ($P< 0.001$).

Conclusion: The combination of swimming training and berberine supplementation had a more pronounced effect in increasing the levels of the mitochondrial-derived peptides MOTS-c and Humanin in the liver of obese diabetic rats. However, interaction effects were not assessed, so statistical synergy cannot be inferred.

Keywords: Type 2 diabetes, Obesity, Swimming exercise, Berberine, MOTS-c, Humanin

QR Code:

Citation: Farsi S. The Effect of 8 Weeks of Swimming Training Combined with Berberine Supplementation on Mitochondrial-Derived Peptides (MOTS-c and Humanin) in the Liver Tissue of Obese Diabetic Rats. , Iran J Diabetes Obes.. 2026; 18 (4) :305-314

URL: http://ijdo.ssu.ac.ir/article-1-1084-en.html
10.18502/ijdo.v18i4.23244

Article info:
Received: 19 December 2025
Revised: 28 June 2026
Accepted: 7 October 2026
This is an open access article under the (CC BY 4.0)

Corresponding Author:
Sirous Farsi, Department of Sports Physiology, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran.
Email: Christopher.simeon@ust.edu.ng

[Downloaded from ijdo.ssu.ac.ir on 2026-11-20]
[DOI: 10.18502/ijdo.v18i4.23244]

Introduction

Type 2 diabetes mellitus (T2DM)and obesity, as global metabolic disorders, are associated with serious complications including hepatic steatosis and insulin resistance (1). The liver plays a pivotal role in regulating glucose and lipid metabolism, and its dysfunction significantly contributes to the pathophysiology of metabolic syndrome (2). In this context, mitochondria are recognized not only as powerhouses but also as important signaling organelles (3). Mitochondrial-derived peptides (MDPs) have emerged as novel metabolic messengers (4). Among these peptides, MOTS-c and Humanin have been extensively studied due to their protective and regulatory roles in metabolism (5). MOTS-c is involved in regulating glucose and fatty acid metabolism (6), while Humanin demonstrates powerful anti-apoptotic and anti-inflammatory effects (7).

Exercise is widely recognized as a powerful non-pharmacological intervention for improving metabolic health. Specifically, endurance exercises such as swimming have been shown to reduce hepatic oxidative stress and induce favorable mitochondrial adaptations (8,9). Interestingly, exercise can act as a stimulus for the secretion of MDPs. Human and animal studies have demonstrated that a single bout of endurance exercise can increase circulating levels of MOTS-c (1,4). A recent study on diabetic rats showed that high-intensity interval training (HIIT) could modulate MOTS-c expression in liver tissue and these changes were associated with improved metabolic markers (5). Furthermore, studies have shown that exercise can act as a potent stimulus for the secretion of mitochondrial peptides (5). Endurance exercises such as swimming increase circulating levels of MOTS-c and Humanin (10,11), One study demonstrated that a single bout of acute endurance exercise can increase plasma levels of these peptides (12).

Alongside exercise, nutritional interventions such as the use of herbal supplements represent a complementary strategy for diabetes management. Berberine, a natural isoquinoline alkaloid extracted from various plants like Berberis, has gained interest for its blood glucose-lowering and insulin-sensitizing properties (6). The mechanisms of action of berberine are pleiotropic and improving mitochondrial function appears to be a key pathway. Studies have shown that berberine can reverse mitochondrial abnormalities induced by a high-fat diet in the liver by activating pathways such as SIRT3 (13). Furthermore, the combination of berberine with aerobic exercise has demonstrated synergistic effects in improving oxidative stress and apoptosis in various tissues, including the liver and heart, in animal models of diabetes (3,7,14).

Material and methods

This research was an experimental study with a controlled laboratory design. In this study, 30 male Wistar rats aged 10-12 weeks with an initial weight of 180-200 grams were used. The animals were kept under standard conditions (temperature 22±2°C, humidity 55±5%, 12:12 hour light-dark cycle). Sample size (n= 6 per group) was determined based on previous similar studies in the field and practical feasibility; no formal a priori power analysis was conducted. The animals were randomly divided into 5 groups (each group of 6): healthy control (HC), obese diabetic (OD), swimming exercise (ODST), berberine (ODB), swimming exercise+berberine (ODST+ODB).

The experimental group rats were fed a high-fat diet (HFD) containing fat (58.4%), carbohydrates (26.6%), and protein (15.0%) for 8 weeks (15,16). At the end of the eighth week, to induce diabetes, streptozotocin (STZ) at a dose of 30 mg/kg body weight in citrate buffer (PH= 4.5) was injected intraperitoneally (17). Five days after injection, fasting blood glucose levels were measured and if the glucose level was above 126 mg/dL on two occasions one week apart, diabetes induction was confirmed (18).

In present study, the swimming training protocol was implemented for 8 weeks

[Downloaded from ijdo.ssu.ac.ir on 2026-11-20]

[DOI: 10.18502/ijdo.v18i4.23244]

according to recognized standards in animal models (19,20). The training was conducted in special rodent swimming pools measuring 80 × 45 × 80 cm. The pools were filled to a depth of 50 cm with warm water (35±1°C), a condition that prevented the rats from using their tails for rest and forced them to swim continuously (20). The first week was the adaptation phase, during which the rats gradually became familiar with the aquatic environment. The training duration gradually increased from 5 minutes on the first day to 10 minutes by the end of the first week. This approach prevented excessive stress in the animals (21).

Weeks 2 to 4 were the basic training phase. During this phase, the training duration was increased weekly and gradually. The exercises were performed without any additional load to allow the rats to fully adapt to the training program (22). Weeks 5 to 8 were the intensity increase phase. Starting from the fifth week, the training load was increased using light weights attached to the rats' tails. These weights were 2% and 5% of the rats' body weight, respectively, used standardly and in accordance with known rodent swimming training protocols (22,23). It is noteworthy that the training conditions were controlled such that all training sessions were conducted at a specific time of day and the water and ambient temperature were continuously monitored. If signs of excessive fatigue were observed, the training was stopped. The details of the eight-week swimming training protocol are presented in Table 1.

Berberine supplement (98% purity) obtained from Sigma-Aldrich was administered daily at a dose of 150 mg/kg body weight, at specific times, as a suspension in distilled water via gavage to the rats in the ODB and ODST+ODB groups. Rats in the other groups received the same amount of distilled water (9). This dose was selected based on previous studies that demonstrated the beneficial effects of berberine on mitochondrial function and glucose metabolism (24).

In this study, after the end of the eight-week intervention period, the data collection process began. Liver tissue sampling was performed 48 hours after the last training session under fasting conditions. For this purpose, the animals were anesthetized with an intraperitoneal injection of a ketamine and xylazine mixture, and then the liver tissue was aseptically removed from their bodies (25). The collected samples were immediately frozen in liquid nitrogen and stored long-term at -80°C. In the laboratory stage, the tissue samples were processed for the assessment of mitochondrial peptides. First, the samples were powdered in a liquid nitrogen environment and then homogenized by adding RIPA lysis buffer containing protease inhibitors. The homogenization process was performed using a vortex and sonication, and then the samples were centrifuged at 10,000 × g for 20 minutes. The supernatant was collected and used for subsequent steps. The total protein concentration of the samples was measured by the Bradford method. For this, Bovine Serum Albumin (BSA) standards at different concentrations were used, and the optical density was read at a wavelength of 595 nm. Based on the plotted standard curve, the protein concentration of the samples was calculated, and all samples were normalized to the same concentration.

For the quantitative assessment of the protein levels of MOTS-c and Humanin peptides in the liver tissue homogenate, commercial ELISA kits specific for the rat species were used according to the manufacturer's instructions. Measurement of MOTS-c was performed using the ELISA kit from Cusabio with a sensitivity of 3.9 pg/mL and a detection range of 15.6 to 1000 pg/mL and the measurement of Humanin was performed using the ELISA kit from ZellBio with a sensitivity of less than 10.0 pg/mL and a detection range of 25 to 800 pg/mL.

All assay steps were performed according to the manufacturer's instructions and at room temperature. After adding the standards and samples to the plate wells, the incubation, washing and secondary antibody addition steps were performed. Finally, after adding TMB substrate and the stop solution, the optical

[Downloaded from ijdo.ssu.ac.ir on 2026-11-20]

[DOI: 10.18502/ijdo.v18i4.23244]

density was measured at a wavelength of 450 nm. The final concentration of the peptides was calculated based on the standard curve and reported as picograms per milligram of total protein.

Statistical methods

Quantitative description of the data was performed using measures of central tendency and dispersion such as mean and standard deviation. The Shapiro-Wilk test was used to determine the normality of the data distribution and Levene's test was used to examine the homogeneity of variances. Furthermore, to investigate significant changes in each of the research variables between the different groups, one-way analysis of variance (ANOVA) was used, and if a statistically significant difference was observed, Tukey's post-hoc test was used to determine the location of the inter-group differences. The significance level for all calculations was considered $p \leq 0.05$. All statistical operations were performed using SPSS software version 32.

Ethical considerations

This study received ethical approval from the Research Ethics Committee of the Islamic Azad University-Marvdasht Branch confirmed this study (IR.AJU.M.REC.1404.569).

Results

Descriptive data related to the levels of mitochondrial peptides MOTS-c and Humanin in liver tissue in different experimental groups are presented in Table 2.

Before data analysis, the assumptions for using parametric tests were examined. The results of the Shapiro-Wilk test showed that the distribution of data for both peptides in all experimental groups was normal ($P> 0.05$ for all cases). Also, the results of Levene's test indicated that the assumption of homogeneity of variances between groups was met (for MOTS-c: $P= 0.247$, for Humanin: $P= 0.114$).

The results of one-way analysis of variance (ANOVA) showed that the interventions had a significant effect on the protein levels of MOTS-c and Humanin in liver tissue (for MOTS-c: $P< 0.001$, $F= 1631.738$; for Humanin: $P= 0.001$, $F= 9.304$).

To determine the exact location of intergroup differences, the Tukey post-hoc test was used. The results of this test for both peptides are presented in Table 3.

The induction of diabetes and obesity led to a significant decrease in MOTS-c levels in the OD group compared to the HC group ($P< 0.0001$). Although ODST and ODB interventions alone led to an increase in the mean levels of this peptide compared to the OD group, this increase was not statistically significant ($P= 0.604$ and $P= 0.748$, respectively). In contrast, the combined intervention (ODST+ODB) significantly increased MOTS-c levels compared to the OD group ($P= 0.003$). However, MOTS-c levels in the combined intervention group remained significantly lower than the HC group ($P< 0.0001$).

The pattern of changes in Humanin was similar to MOTS-c. The levels of this peptide in the OD group showed a significant decrease compared to the HC group ($P= 0.001$). ODST and ODB interventions alone, despite showing an increasing trend, failed to create a statistically significant change in Humanin levels ($P= 0.13$ and $P= 0.12$, respectively). However, the combination of these two interventions (ODST+ODB) led to a significant increase in Humanin levels compared to the diabetic group ($P= 0.02$). The difference between the combined intervention group and the healthy control group was not significant ($P= 0.08$).

Discussion

The findings of the present study investigated the effects of eight weeks of swimming training and berberine supplementation on hepatic levels of mitochondrial-derived peptides (MDPs), including MOTS-c and Humanin, in obese diabetic rats.

[Downloaded from ijdo.ssu.ac.ir on 2026-11-20]

[DOI: 10.18502/ijdo.v18i4.23244]

Table 1. Eight-week swimming training protocol for obese diabetic rats

Training Intensity	**Load** (% Body Weight)	**Duration** (minutes)	**Week**
Adaptation: Gradual increase from 5 to 10 min	0	10	1
Basic Intensity: Swimming without load	0	15	2
Basic Intensity: Swimming without load	0	20	3
Basic Intensity: Swimming without load	0	25	4
Increased Intensity: Addition of 2% load	2	30	5
Increased Intensity: Addition of 2% load	2	35	6
Increased Intensity: Addition of 5% load	5	40	7
Increased Intensity: Addition of 5% load	5	45	8

HFD: High-Fat Diet, STZ: Streptozotocin, ODST: Obese Diabetic + Swimming Training, ODB: Obese Diabetic + Berberine, ODST+ODB: Obese Diabetic + Swimming Training + Berberine.

Table 2. Descriptive Indices of MOTS-c and Humanin Peptides (pg/mg protein)

Group	MOTS-c (Mean ± SD)	Humanin (Mean ± SD)
HC	90.54 (± 0.29)	60.36 (± 0.57)
OD	67.93 (± 0.80)	56.02 (± 1.16)
ODST	68.43 (± 0.20)	57.79 (± 1.38)
ODB	68.35 (± 0.29)	57.82 (± 1.84)
ODST+ODB	69.35 (± 0.96)	58.42 (± 0.91)

HC: Healthy Control, OD: Obese Diabetic, ODST: Obese Diabetic + Swimming Training, ODB: Obese Diabetic + Berberine, ODST+ODB: Obese Diabetic + Swimming Training + Berberine, SD: Standard Deviation.

Table 3. Results of tukey's post-hoc test for comparing peptide levels between different groups

Peptide	Group (I)	Group (J)	Significance Level
MOTS-c	HC	OD	< 0.0001
		ODST	< 0.0001
		ODB	<0.0001
		ODST+ODB	< 0.0001
	OD	ODST	0.604
		ODB	0.748
		ODST+ODB	0.003
	ODST	ODB	0.99
		ODST+ODB	0.09
	ODB	ODST+ODB	0.055
Humanin	HC	OD	0.001
		ODST	0.01
		ODB	0.01
		ODST+ODB	0.08
	OD	ODST	0.13
		ODB	0.12
		ODST+ODB	0.02
	ODST	ODB	0.99
		ODST+ODB	0.90
	ODB	ODST+ODB	0.91

HC: Healthy Control, OD: Obese Diabetic, ODST: Obese Diabetic + Swimming Training, ODB: Obese Diabetic + Berberine, ODST+ODB: Obese Diabetic + Swimming Training + Berberine, MOTS-c: Mitochondrial Open Reading Frame of the 12S rRNA-c. Significance levels are P-values from Tukey's post-hoc test.

The main findings revealed that the induction of diabetes and obesity led to a significant decrease in both mitochondrial peptides.

While none of the interventions alone could significantly reverse this decrease, the combined intervention successfully and significantly increased the levels of both peptides compared to the diabetic group.

These results highlight the potential benefit of combining physical activity with phytochemical supplementation to modulate

[Downloaded from ijdo.ssu.ac.ir on 2026-11-20]

[DOI: 10.18502/ijdo.v18i4.23244]

key mitochondrial signaling molecules in a disrupted metabolic state.

Our data clearly show that the OD group exhibited significantly lower hepatic levels of both MOTS-c and Humanin peptides compared to the HC group. This finding aligns with growing evidence linking metabolic disorders to mitochondrial dysfunction and impaired MDP signaling (1,26). Mitochondria play a central role in energy metabolism and cellular stress responses and their dysfunction is a hallmark of insulin resistance and fatty liver disease (2,26). The observed decrease in MDP levels in the diabetic state may reflect a failure in adaptive mitochondrial signaling, potentially exacerbating the worsening metabolic disorder. Strong evidence indicates that MOTS-c improves glucose metabolism and insulin sensitivity (6,27), while Humanin exerts potent cytoprotective effects against apoptosis and inflammation (4,7). Therefore, their deficiency in the liver could contribute to the progression of hepatic complications in diabetes and obesity.

The primary aim of this study was to evaluate the efficacy of non-pharmacological interventions, namely swimming exercise and berberine, in countering this MDP deficiency. Exercise is a known inducer of mitochondrial biogenesis and function (3). Previous research has shown that acute endurance exercise can increase circulating levels of MOTS-c and Humanin (10,12). Similarly, chronic endurance training has been shown to increase serum levels of MDPs in professional athletes (11).

In our study, the swimming training group (ODST) showed a non-significant increasing trend in both peptides compared to the OD group. This suggests that while the applied training protocol was a strong physiological stimulus, it might not have been sufficient to fully restore the severely reduced MDP levels in this specific model of combined obesity and diabetes. The progressive protocol, including the addition of weighted swimming, was designed to induce adaptation (19,20); however, the profound metabolic disruption in the OD group may have required a more potent intervention for a significant independent effect.

Similarly, the ODB group also failed to produce a statistically significant increase in hepatic MOTS-c or Humanin, despite its known benefits on glucose metabolism and mitochondrial function. Berberine has been reported to reverse high-fat diet-induced mitochondrial abnormalities in the liver, possibly through activation of pathways such as SIRT3 (28). Other studies have shown that berberine can protect against diabetic nephropathy by promoting mitochondrial energy homeostasis (14). The lack of a significant independent effect in our study could be related to the severity of the underlying metabolic pathology. It is possible that berberine's primary action in this context was improving the overall metabolic environment, which may be a prerequisite for increasing MDP levels, but is not sufficient as a standalone stimulus.

The most compelling finding of this research is the significant increase in the levels of both MOTS-c and Humanin peptides by the combined intervention (ODST+ODB group). This enhanced effect may be mediated, at least in part, via activation of the AMPK/PGC-1α pathway. Exercise is a powerful physiological stressor that is known to activate multiple signaling pathways, including AMPK and PGC-1α, which are key regulators of metabolism and mitochondrial biogenesis (5,29).

MOTS-c has been shown to interact with exercise intervention to regulate PGC-1α expression and improve insulin resistance, likely through the AMPK signaling pathway (24). On the other hand, various studies have reported that berberine can activate AMPK (14,28). Therefore, this combination may result in stronger and more sustained activation of AMPK and its downstream targets, creating a more favorable environment for the production and/or release of MDPs.

Furthermore, both interventions have been reported to possess antioxidant and anti-inflammatory properties. Swimming training has been shown to reduce hepatic oxidative

[Downloaded from ijdo.ssu.ac.ir on 2026-11-20]

[DOI: 10.18502/ijdo.v18i4.23244]

stress (13), while berberine demonstrates anti-inflammatory effects (4,28).

Given that oxidative stress and inflammation are key factors in mitochondrial dysfunction in diabetes (2,26), their concurrent reduction might have contributed to the restoration of mitochondrial health and, consequently, MDP signaling. However, as these pathways were not directly measured in the present study, this interpretation remains speculative. The improvement in Humanin levels is particularly noteworthy, as this peptide is a potent inhibitor of apoptosis (4,7).

Its restoration in the combined group indicates improved signaling for the survival of liver cells, which could be a key mechanism for the previously reported benefits of berberine and aerobic exercise in improving oxidative stress and apoptosis in liver tissue in animal models of diabetes (14).

For MOTS-c, the levels of this peptide in the combined group, although significantly higher than the OD group, remained statistically lower than the HC group. This observation suggests that despite the effectiveness of the combined therapy, the eight-week intervention period was likely unable to fully restore MOTS-c signaling to the non-diabetic baseline state. In contrast, Humanin levels in the combined group were not significantly different from the HC group, indicating a more complete recovery of this specific cytoprotective peptide. This dissociated effect requires further investigation but could reflect distinct regulatory pathways or different sensitivities of these MDPs to metabolic disturbances and therapy.

Several limitations of this study should be acknowledged. First, despite using a well-established animal model of obesity and diabetes, we did not measure hepatic functional markers such as ALT and AST, nor did we perform histological assessments (e.g., steatosis and inflammation scoring) to directly evaluate liver pathology.

Second, the sample size (n= 6 per group) was determined based on previous similar studies and feasibility, without a priori power analysis; therefore, the findings should be interpreted with caution. Third, while we observed alterations in MDP levels, we did not measure key metabolic parameters such as HbA1c, serum insulin, HOMA-IR, or final body weight, which limits our ability to directly correlate peptide changes with the severity of metabolic disturbance. Fourth, although the discussion refers to molecular pathways including AMPK/PGC-1α and SIRT3, these were not directly measured by Western blot or qPCR in the present study. Consequently, mechanistic interpretations should be considered speculative and are provided to guide future investigations.

Conclusion

The combination of swimming training and berberine supplementation significantly increased the levels of the mitochondrial-derived peptides MOTS-c and Humanin in the liver of obese diabetic rats compared with the untreated obese diabetic group, whereas neither intervention alone produced a significant change. However, the combined group did not differ significantly from either single-intervention group and interaction effects were not assessed; therefore, statistical synergy cannot be concluded. Studies with a factorial design are needed to clarify possible interactions.

Acknowledgements

The authors would like to thank the staff of the Laboratory Animal Center for their technical assistance during the experimental procedures.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

Authors' contributions

[Downloaded from ijdo.ssu.ac.ir on 2026-11-20]

[DOI: 10.18502/ijdo.v18i4.23244]

S.F: Conceptualization, study design, data collection, formal analysis, investigation, writing–original draft, writing–review & editing, supervision, project administration.

[Downloaded from ijdo.ssu.ac.ir on 2026-11-20]

[DOI: 10.18502/ijdo.v18i4.23244]

References

1. Kim H, Lee DS, An TH, Park HJ, Kim WK, Bae KH, et al. Metabolic spectrum of liver failure in type 2 diabetes and obesity: from NAFLD to NASH to HCC. International journal of molecular sciences. 2021;22(9):4495.
2. Di Ciaula A, Passarella S, Shanmugam H, Noviello M, Bonfrate L, Wang DQ, et al. Nonalcoholic fatty liver disease (NAFLD). Mitochondria as players and targets of therapies?. International Journal of Molecular Sciences. 2021;22(10):5375.
3. Merry TL, Chan A, Woodhead JS, Reynolds JC, Kumagai H, Kim SJ, et al. Mitochondrial-derived peptides in energy metabolism. American Journal of Physiology-Endocrinology and Metabolism. 2020;319(4):E659-66.
4. Kal S, Mahata S, Jati S, Mahata SK. Mitochondrial-derived peptides: Antidiabetic functions and evolutionary perspectives. Peptides. 2024;172:171147.
5. Woodhead JS, Merry TL. Mitochondrial-derived peptides and exercise. Biochimica et Biophysica Acta (BBA)-General Subjects. 2021;1865(12):130011.
6. Kong BS, Lee C, Cho YM. Mitochondrial-encoded peptide MOTS-c, diabetes, and aging-related diseases. Diabetes & metabolism journal. 2023;47(3):315-24..
7. Mehta HH, Xiao J, Ramirez R, Miller B, Kim SJ, Cohen P, et al. Metabolomic profile of diet-induced obesity mice in response to humanin and small humanin-like peptide 2 treatment: HH Mehta et al. Metabolomics. 2019;15(6):88.
8. Habibian M, Khosravi M. The Effect of 8 Weeks Regular Swimming Exercise on The Cardiac Levels of Matrix Mettaloproteinase-2 and Transforming Growth Factor-B1 In Diabetic Rats. Iranian Journal of Diabetes and Metabolism. 2016; 15 (2) :67-74. http://ijdld.tums.ac.ir/article-1-5342-en.html.(in Persian)
9. Zhang YP, Deng YJ, Tang KR, Chen RS, Liang S, Liang YJ, et al. Berberine ameliorates high-fat diet-induced non-alcoholic fatty liver disease in rats via activation of SIRT3/AMPK/ACC pathway. Current medical science. 2019;39(1):37-43.
10. Woodhead JS, D'Souza RF, Hedges CP, Wan J, Berridge MV, Cameron-Smith D, et al. High-intensity interval exercise increases humanin, a mitochondrial encoded peptide, in the plasma and muscle of men. Journal of applied physiology. 2020;128(5):1346-54.
11. Alser M, Ramanjaneya M, Anwardeen NR, Donati F, Botrè F, Jerobin J, et al. The effect of chronic endurance exercise on serum levels of MOTS-c and humanin in professional athletes. Reviews in Cardiovascular Medicine. 2022;23(5):181.
12. von Walden F, Fernandez-Gonzalo R, Norrbom J, Emanuelsson EB, Figueiredo VC, Gidlund EK, et al. Acute endurance exercise stimulates circulating levels of mitochondrial-derived peptides in humans. Journal of Applied Physiology. 2021;131(3):1035-42.
13. Lima FD, Stamm DN, Della-Pace ID, Dobrachinski F, de Carvalho NR, Royes LF, et al. Swimming training induces liver mitochondrial adaptations to oxidative stress in rats submitted to repeated exhaustive swimming bouts. PloS one. 2013;8(2):e55668.
14. Mehrpuya E, Keshavarz S, Banitalebi E, Naghizadeh H, Ramezani J. Effects of Aerobic Exercise Combined with Berberine Chloride Hydrate Supplementation on the Mitochondrial Biogenesis of Cardiac Muscles in Diabetic Male Rats. Zahedan Journal of Research in Medical Sciences. 2023;25(4):1-9.
15. Pekkala S, Rafiei MM, Eslami Z, Ghaderi M, Moghanlou AE, Sharifian S, et al. High-intensity interval training and moderate intensity training with exogenous adenosine counteract development of obesity in rats. Science & Sports. 2022;37(5-6):477-85.
16. Gilani A, Pandey V, Garcia V, Agostinucci K, Singh SP, Schragenheim J, et al. High-fat diet-induced obesity and insulin resistance in CYP4a14−/− mice is mediated by 20-HETE. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2018;315(5):R934-44.
17. Costa LR, Castro CA, Marine DA, Fabrizzi F, Furino VD, Malavazi I, et al. High-intensity interval training does not change vaspin and omentin and does not reduce visceral adipose tissue in obese rats. Frontiers in Physiology. 2021;12:564862.
18. Du J, Shen L, Tan Z, Zhang P, Zhao X, Xu Y, et al. Betaine supplementation enhances lipid metabolism and improves insulin resistance in mice fed a high-fat diet. Nutrients. 2018;10(2):131.
19. Lunz W, Peluzio MC, Dias CM, Moreira AP, Natali AJ. Long-term aerobic swimming training by rats reduces the number of aberrant crypt foci in 1, 2-dimethylhydrazine-induced colon cancer. Brazilian Journal of Medical and Biological Research. 2008;41(11):1000-4.
20. Fei Z, Li D, Li K, Zhou M, Li Y, Li Y, Sun Z. Detraining after tumor-bearing accelerates tumor growth while continuous training decreases tumor growth in mice. Journal of Traditional Chinese Medical Sciences. 2020;7(1):75-81.

[Downloaded from ijdo.ssu.ac.ir on 2026-11-20]

[DOI: 10.18502/ijdo.v18i4.23244]

21. Ramos DS, Olivo CR, Quirino SL, Fernanda DT, Toledo AC, Martins MA, et al. Low-intensity swimming training partially inhibits lipopolysaccharide-induced acute lung injury. Medicine & Science in Sports & Exercise. 2010;42(1):113-9.
22. Xu X, Ding Y, Yang Y, Gao Y, Sun Q, Liu J, et al. β-glucan salecan improves exercise performance and displays anti-fatigue effects through regulating energy metabolism and oxidative stress in mice. Nutrients. 2018;10(7):858.
23. Paceli RB, Cal RN, dos Santos CH, Cordeiro JA, Neiva CM, Nagamine KK, et al. The influence of physical activity in the progression of experimental lung cancer in mice. Pathology-Research and Practice. 2012;208(7):377-81.
24. Guo Q, Chang B, Yu QL, Xu ST, Yi XJ, Cao SC. Adiponectin treatment improves insulin resistance in mice by regulating the expression of the mitochondrial-derived peptide MOTS-c and its response to exercise via APPL1–SIRT1–PGC-1α. Diabetologia. 2020;63(12):2675-88.
25. Tayebi SM, Motaghinasab S, Eslami R, Ahmadabadi S, Basereh A, Jamhiri I. Impact of 8-week cold-and warm water swimming training combined with cinnamon consumption on serum METRNL, HDAC5, and insulin resistance levels in diabetic male rats. Heliyon. 2024;10(8):e29742.
26. Alimujiang M, Yu XY, Yu MY, Hou WL, Yan ZH, Yang Y, et al. Enhanced liver but not muscle OXPHOS in diabetes and reduced glucose output by complex I inhibition. Journal of Cellular and Molecular Medicine. 2020;24(10):5758-71.
27. Yang B, Yu Q, Chang B, Guo Q, Xu S, Yi X, et al. MOTS-c interacts synergistically with exercise intervention to regulate PGC-1α expression, attenuate insulin resistance and enhance glucose metabolism in mice via AMPK signaling pathway. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2021;1867(6):166126.
28. Qin X, Jiang M, Zhao Y, Gong J, Su H, Yuan F, et al. Berberine protects against diabetic kidney disease via promoting PGC-1α-regulated mitochondrial energy homeostasis. British Journal of Pharmacology. 2020;177(16):3646-61.
29. Gurd BJ, Menezes ES, Arhen BB, Islam H. Impacts of altered exercise volume, intensity, and duration on the activation of AMPK and CaMKII and increases in PGC-1α mRNA. InSeminars in Cell & Developmental Biology. 2023;143:17-27.

[Downloaded from ijdo.ssu.ac.ir on 2026-11-20]

[DOI: 10.18502/ijdo.v18i4.23244]