KMANPUB | Health Nexus Vol. 4 No. 1 (2026): 1-8

Article history:
Received 11 September 2025
Revised 22 November 2025
Accepted 16 December 2025
Initial Published 29 December 2025
Final Publication 01 January 2026

Effects of Aerobic Exercise at Different Circadian Phases on p53 Expression and β-Cell Survival in the Pancreas of Type 2 Diabetic NMRI Mice

Fatemeh Sepehrinya[1], Maryam Janbozorgi[2*], Asma Taheri[2], Masoumeh Hosseinzadeh[3]

[1] Graduate of Exercise Physiology, Shahid Chamran University of Ahvaz, Iran
[2] Assistant Professor, Department of Sport Physiology, Faculty of Sport Sciences, Shahid Chamran University of Ahvaz, Ahvaz, Iran
[3] Instructor, Department of Sport Physiology, Faculty of Sport Sciences, Shahid Chamran University of Ahvaz, Ahvaz, Iran

*** Corresponding author email address**: m.janbozorgi@scu.ac.ir

A r t i c l e I n f o

Article type:
Original Research

How to cite this article:
Sepehrinya, F., Janbozorgi, M., Taheri, A., & Hosseinzadeh, M. (2026). Effects of Aerobic Exercise at Different Circadian Phases on p53 Expression and β-Cell Survival in the Pancreas of Type 2 Diabetic NMRI Mice. *Health Nexus*, *4*(1), 1-8.
https://doi.org/10.61838/kman.hn.4828

A B S T R A C T

Circadian rhythms regulate glucose homeostasis, insulin secretion, mitochondrial function, and apoptosis in pancreatic β-cells. The tumor suppressor gene p53 is a key molecular regulator of apoptosis and may contribute to β-cell loss in type 2 diabetes (T2DM). This study investigates the effects of aerobic exercise performed during different circadian phases on blood glucose, β-cell survival, insulin presence, and p53 gene expression in type 2 diabetic NMRI mice. Thirty male NMRI mice were assigned to six groups: healthy controls (CH-ZT3, CH-ZT15), diabetic controls (CD-ZT3, CD-ZT15), and diabetic exercise groups trained in light (TD-ZT3) or dark phase (TD-ZT15). T2DM was induced via high-fat diet plus low-dose streptozotocin. Aerobic training (50–60% Vmax) was performed for 8 weeks. Pancreatic tissues were analyzed for β-cell survival, insulin immunostaining, and p53 expression via qRT-PCR. Data were evaluated using two-way ANOVA. Exercise significantly reduced glucose levels ($p < 0.05$), increased β-cell survival ($p < 0.0001$), and decreased p53 expression ($p < 0.0001$). Light-phase training (ZT3) produced greater improvements than dark-phase training. A significant interaction between training × circadian phase was found for β-cell percentage and p53 expression ($p < 0.01$). Aerobic exercise improves β-cell viability and reduces apoptotic signaling in diabetic mice, with circadian phase strongly modulating the benefits. Exercise during the light phase showed superior outcomes, suggesting that timing of physical activity may be an important factor in diabetes management.

Keywords: *Circadian Rhythm, Aerobic Exercise, Type 2 Diabetes, p53 Gene Expression, Pancreatic β-Cells, NMRI Mice*

1. Introduction

Type 2 diabetes mellitus (T2DM) is characterized by chronic hyperglycemia resulting from insulin resistance and progressive β-cell failure. β-cell apoptosis is a major contributor to declining insulin production, and molecular regulators such as p53 play key roles in mediating stress-induced cell death pathways. Elevated glucose levels, inflammatory cytokines, and oxidative stress activate p53, leading to β-cell dysfunction and apoptosis (1-3).

Oxidative stress (increased blood sugar, inflammatory response, and insulin resistance) can affect β cells. Studies have shown that stress leads to significant changes in β cell chromatin accessibility, which causes significant changes in gene expression, chronic hyperglycemia, progressive reduction in β cell mass, and increased apoptosis of these

cells (4). Ghorbanzadeh et al. (2017) examined the relationship between pancreatic tissue apoptosis and voluntary exercise in mice with T2DM and reported a significant decrease in p53 levels and pancreatic apoptosis. Voluntary exercise has anti-apoptotic effects on pancreatic tissue of T2DM mice, and these protective effects are likely achieved through the reduction of glucose and HbA1c levels (5). Also, Safdar et al. (2015) suggested that aerobic exercise reduces multisystem pathology and increases the lifespan of mice by affecting mitochondria. They reported that p53 is translocated to mitochondria and facilitates mitochondrial repair and biogenesis in response to aerobic exercise. In fact, aerobic exercise reduces telomere attrition, aberrant p53 signaling, and pathological levels of apoptosis (6). Curran et al. (2020) also examined the effects of short-term exercise on β-cell health and concluded that short-term exercise improves β-cell mass and function in human and animal models. The initial improvement in function is observed through increased insulin content in β-cells and their ability to secrete insulin in response to glucose stimulation (7).

Circadian rhythms influence metabolic function and gene expression throughout the body. Central and peripheral clocks regulate insulin secretion, glucose uptake, mitochondrial efficiency, and redox balance (8, 9). Misalignment between circadian rhythms and metabolic activity exacerbates insulin resistance and β-cell stress (10). Rodent studies show that exercise outcomes differ depending on timing, with enhanced insulin sensitivity and glucose handling occurring during specific circadian windows (11).

Exercise is widely recognized as one of the most effective non-pharmacological interventions for improving glycemic control. It enhances mitochondrial biogenesis, insulin sensitivity, anti-inflammatory responses, and reduces apoptotic signaling (12-14). However, whether these beneficial effects are optimized by performing exercise at specific circadian phases remains unclear.

Given the central role of p53 in apoptosis and β-cell dysfunction, and the known effects of circadian rhythms on metabolism, this study examines how aerobic exercise performed in the light vs. dark phase impacts glycemic control, β-cell survival, insulin presence, and p53 expression in type 2 diabetic NMRI mice.

2. Methods and Materials

2.1. Animals

Thirty male NMRI mice (26 ± 3.22 grams) were obtained and housed in standard cages under a controlled 12:12 h light-dark cycle (lights on at 6:00, lights off at 18:00), temperature 22 ± 2 °C, with free access to food and water.

Type 2 diabetes was induced using:

High-fat diet (HFD 60%) for 5 weeks

Low-dose streptozotocin (20 mg/kg) intraperitoneal for 3 consecutive days

Mice with fasting glucose > 126 mg/dl were considered diabetic.

2.2. Training Protocol

Exercise was conducted at two distinct time points during the day. The timing of the exercise sessions was determined according to the protocol established by Sato et al. (2019) in Cell Metabolism, with lights-on at 6:00 AM (ZT0) and lights-off at 6:00 PM (ZT12). Training sessions were scheduled three hours after lights-on (9:00 AM, ZT3) and three hours after lights-off (9:00 PM, ZT15) (15).

Prior to the main training intervention, mice underwent a one-week treadmill adaptation period to ensure gradual acclimation. The subsequent exercise regimen was performed at moderate intensity, corresponding to 50–60% of maximal running capacity (Vmax), with each session lasting 80 minutes. This program was implemented over eight consecutive weeks, with five sessions per week conducted at the predetermined time points (16).

Measurement of insulin resistance index: To calculate the insulin resistance index (HOMA-IR), blood glucose was assessed by glucose oxidase and spectrophotometry (Pars Azmoun, Iran, and insulin was assessed by species-specific ELISA (Bioassay Technology, China) with an interassay accuracy of 3.4% and an intraassay accuracy of 4.3%. The following formula was used to measure insulin resistance:

Homa-IR= (Fasting Insulin(μU/ml) *Fasting Glucose(mmol/L))/22.5

An increase or decrease in HOMA-IR in diabetic subjects compared to healthy mice was considered to indicate an increase or decrease in insulin resistance, respectively.

Health Nexus
E-ISSN: 2981-2569

2.3. *Immunohistochemically Assessment of Pancreatic β-Cells*

specific markers in pancreatic tissue sections. Following standard deparaffinization and rehydration procedures, antigen retrieval was performed using a citrate-based buffer system under heat-induced epitope retrieval (HIER) conditions. Endogenous peroxidase and nonspecific epitopes were blocked prior to antibody incubation to ensure specificity and to reduce background fluorescence.

Primary antibodies against β-cell markers were applied at dilutions recommended by the manufacturers, and incubation conditions were optimized based on antibody characteristics. Fluorescently labeled secondary antibodies commonly conjugated with CY3 (red) or FITC (green) were used to visualize target antigens. Nuclear counterstaining was performed using DAPI to facilitate structural orientation. After standard dehydration and mounting procedures, slides were imaged using a fluorescent microscope equipped with a digital camera system.

For quantitative assessment, multiple randomly selected microscopic fields were analyzed. The percentage of positively stained regions was calculated using Microbin software, and quantitative results were expressed as mean ± SEM. To allow relative comparisons, values were normalized to the control group and reported as fold-change versus control (17).

2.4. *Real-Time Quantitative RT-PCR*

To evaluate changes in the expression level of p53 gene, realtime PCR was performed using qPCRTM Green Master Kit for SYBR Green I (Jena Biosciense, Germany) on a Lightcycl Detection System (Roche, USA). Relative expression level of the p53 transcripts were compared to rat GAPDH as housekeeping gene.

Reactions were performed in a 12.5 ll mixture containing 6.25 ll qPCRTM Green Master Kit for SYBR Green I (Jena Biosciense, Germany), 0.25 ll of each primer (200 nM), 3 ll cDNA (100 ng), and 2.25 ll nuclease-free water. The PCR protocol used consisted of a 5 min denaturation at 94 C followed by 45 cycles of 94 C for 15 s, 60 C for 30 s. Reactions were performed in triplicate. Two separate reactions without cDNA or with RNA were performed in parallel as controls. Relative quantification was performed according to the comparative 2-DDCt method and using Lightcycler 96 software. All qPCR analysis was performed according to The minimum information for publication of quantitative real-time PCR experiments (MIQE) guideline (18).

2.5. *Primer Design*

The sequences P53 and GAPDH genes were obtained from NCBI database and primer sets were designed via GeneRunner and Primer Express software v.3.0 (Applied Biosystems, Foster City, USA) and analyzed in Basic Local Alignment Search Tool to avoid homology with other genome region. Oligonucleotid sequences are shown in Table 1.

Table 1

Characteristics of primers which were used for Real-Time PCR analysis.

GENE NAME	SEQUENCE	accession NO
P53-Mice-F	GGCTCCGACTATACCACTATCC	NM_000546.6
P53-Mice-R	GAGTCTTCCAGCGTGATGATG	
GAPDH-mice-F	CATCACTGCCACCCAGAAGACTG	NM_008084
GAPDH-mice-R	ATGCCAGTGAGCTTCCCGTTCAG	

2.6. *Statistical Analysis*

Two-way ANOVA evaluated effects of training, circadian phase, and interaction. Tukey post-hoc test was applied. Significance was set at $p < 0.05$.

3. Findings and Results

Analysis of variance of the findings of the present study are presented in Table 2. The results show that the effect of aerobic exercise on the desired parameters of diabetic mice

Health Nexus
E-ISSN: 2981-2569

is significant at the one percent level. Comparison of the mean of the evaluated variables, after the intervention, in the different research groups is presented in Table 3.

Table 2

Analysis of variance of the evaluated parameters

	Weight (Gr)	Homa-IR (µU/ml*mmol/l)	Insulin (mU/L)	Glucose (Mg/dl)
F	5.455**	66.823**	51/422**	22/217**
p value	0.008	0.000	0.000	0.000

Table 3

Mean and standard deviation of the studied variables after intervention

	Weight (Gr)	Homa-IR (µU/ml*mmol/l)	Insulin (mU/L)	Glucose (Mg/dl)	Vmax (m/min)
CH-ZT3	33.00±3.60 b	9.99±0.85 f	40.08±3.61 e	101.18±4.10 e	15.16±1.04 b
CH-ZT15	34.00±2.64 b	11.83±1.74 e	41.10±5.25 e	116.40±4.22 d	15.50±1.32 b
CD-ZT3	41.33±1.52 a	31.17±0.79 b	88.04±5.36 b	143.58±5.09 b	14.83±1.60 b
CD-ZT15	40.66±3.05 a	37.80±3.04 a	97.53±6.43 a	157.33±5.45 a	15.60±0.91 b
TD-ZT3	34.33±1.52 b	25.27±3.38 c	71.32±7.12 c	143.20±5.63 b	24.66±1.15 a
TD-ZT15	36.33±1.55 b	20.10±2.60 d	63.80±5.87 d	127.40±3.36 c	24.80±1.70 a

Non-identical Latin letters above the columns indicate that their differences are significant in the LSD post hoc test. CH-ZT3 = healthy control group light phase, CH-ZT15 = healthy control group dark phase, CD-ZT3 = diabetic control group light phase, CD-ZT15 = diabetic control group dark phase, TD-ZT3 = diabetic exercise group light phase, TD-ZT15 = diabetic exercise group dark phase. HOMA-IR: Index of insulin resistance.

The results of the post hoc test between the study groups (Table 2) showed a significant increase in the levels of glucose, insulin, HOMA-IR and weight in diabetic mice compared to healthy control mice (P < 0.05). The effect of aerobic training on the changes in the levels of these variables in the training groups compared to the diabetic groups was significant, and the decreasing trend in the levels of these variables in the trained mice was significant (P < 0.05). The changes in the levels of glucose, insulin and HOMA-IR variables in the two dark and light phases in all the study groups showed a significant difference (P < 0.05). However, the changes in weight in the two dark and light phases were not significant (P > 0.05). The evaluation of the changes in maximum speed between the study groups showed a significant effect of aerobic training on increasing the maximum speed in the trained mice compared to the other groups (P < 0.05). Changes in maximum speed in the two phases of darkness and light were not significant (P > 0.05)

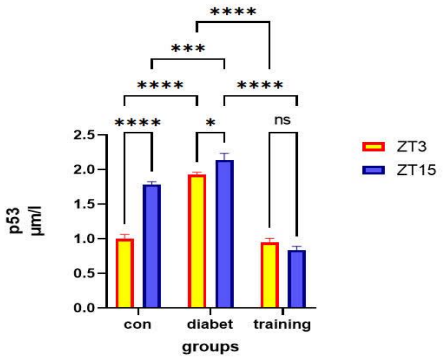

Figure 1

p53 gene level expressed in different groups. Data are mean ± SD. pairwise comparisons Between bars indicates rate of significant difference at p\0.05

Health Nexus
E-ISSN: 2981-2569

Two-way analysis of variance was performed to investigate the effects of training groups and time (light/dark phase) on p53 gene expression. The results showed that all three factors including training (Training), time (Time) and their interaction (Training × Time) had statistically significant effects on p53 gene expression ($P < 0.0001$). As shown in **Error! Reference source not found.**, a significant difference was observed between the training and control groups ($P < 0.0001$), indicating a significant effect of training on p53 gene expression. In particular, the diabetic training groups (TD-ZT3) and (TD-ZT15) showed a significant increase in the expression level of this gene compared to the diabetic and healthy control groups. The light and dark phase also had a significant effect on p53 gene expression ($P < 0.0001$). This finding indicates circadian rhythm-dependent changes in p53 gene expression. Analysis of the interaction of exercise and time showed that the effect of exercise on p53 gene expression was time (light/dark phase) dependent ($P < 0.0001$). In other words, the response of the p53 gene to exercise is different in the light and dark phases, and this difference is also evident between the diabetic and healthy groups.

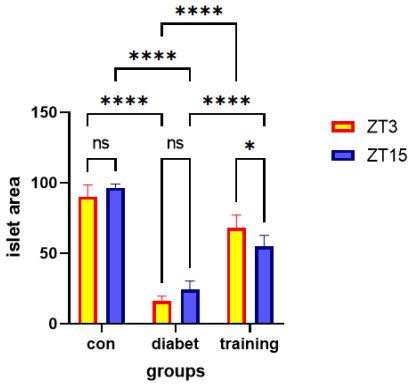

Figure 2

Percentage of viable cells in pancreatic tissue of different groups. Data are mean ± SD. pairwise comparisons Between bars indicates rate of significant difference at p\0.05

The results of two-way ANOVA showed that exercise training had a highly significant effect on the percentage of viable cells in the tissue ($p < 0.0001$), while time (ZT3) compared to ZT15 () alone did not make a difference ($p = 0.8664$). The interaction effect of exercise and time was also significant ($p = 0.0023$), meaning that the tissue response to exercise was dependent on the circadian phase. As can be seen in **Error! Reference source not found.**, the percentage of viable cells in the diabetic group was significantly reduced, and exercise training was able to significantly increase this index ($p < 0.0001$), although its level did not yet reach the level of the healthy control group. In addition, the increase caused by exercise was more pronounced in the light phase (ZT3) than in the dark phase (ZT15), indicating the role of exercise timing in improving cell survival and function. Therefore, the second hypothesis is confirmed.

4. Discussion

The present study demonstrates that aerobic exercise significantly improves pancreatic β-cell survival, reduces p53 expression, and enhances glycemic control in type 2 diabetic NMRI mice, with the magnitude of these effects strongly dependent on circadian timing. Light-phase training (ZT3) induced greater improvements than dark-phase training (ZT15), indicating that the timing of exercise can critically influence molecular and functional outcomes.

In diabetes, hyperglycemia activates the AKT pathway, which activates MDM2 through phosphorylation. On the

Health Nexus
E-ISSN: 2981-2569

other hand, hyperglycemia induces p53 by inducing oxidative stress. These events result in the formation of the MDM2-p53 complex, which prevents p53 degradation. p53 then translocated to mitochondria, where it induces cytochrome c release by lowering its membrane potential, which ultimately reduces beta cell mass. In addition, the inhibition of p53 leads to the suppression of pyruvate carboxylase (PC). These changes in TCA cycle metabolism create conditions for impaired oxygen consumption, which ultimately leads to mitochondrial dysfunction and reduced GSIS. Even a small increase in p53 has the ability to suppress GSIS, and in advanced stages of diabetes, upregulation of p53 leads to β cell apoptosis and increased blood glucose levels (19). A number of signaling pathways in the regulation of beta cell function depend on p53. Free fatty acids (FFA) promote apoptosis in β cells through activation of AKT and also increase p16 expression in these cells (20). In the normal state, AKT acts as a major inhibitor of p53 by phosphorylating and activating MDM2 and prevents its-dependent cell death (21). One of the pathways that causes β cell death following high-fat diets is the activation of p53 (19). The presence of p53 not only makes β cells more sensitive to apoptosis, but also suppresses the insulin pathway and disrupts its secretion (21). Indeed, FFAs, reactive oxygen species and inflammatory cytokines are upstream of p53 and, by stimulating it, induce β cell apoptosis (21). p53 binds to DNA and activates the WAF1 gene, which results in the production of the protein p21. P21 inhibits cell proliferation and induces cellular senescence (22). Inactivation of p53 requires its phosphorylation by MAPK and ATM. This conformational change causes p53 to dissociate from MDM2, translocate to the cytoplasm, and decrease its activity (22).

Consistent with previous studies, aerobic exercise reduced fasting glucose levels, particularly in the light-phase group. This is supported by findings that exercise enhances GLUT4 translocation, improves insulin sensitivity, and increases skeletal muscle glucose uptake (13). Rodents exhibit circadian variations in glucose tolerance, with enhanced insulin responsiveness during the rest (light) phase (9). Thus, performing exercise during this window may amplify metabolic benefits.

β-cell percentage was markedly reduced in diabetic controls, reflecting apoptosis induced by glucotoxicity and oxidative stress. Exercise increased β-cell survival, particularly in the TD-ZT3 group. Circadian modulation may underlie this effect: studies show that CLOCK/BMAL1 activity fluctuates across the day, influencing mitochondrial dynamics, ATP production, antioxidant defense, and β-cell proliferation (8, 9). Exercise during phases of high cellular repair capacity may facilitate β-cell recovery.

p53 is activated by oxidative stress, DNA damage, and inflammatory cytokines, and promotes β-cell apoptosis via BAX activation and mitochondrial pathway signaling (2, 3). Elevated p53 in diabetic mice aligns with patterns reported in diabetic islets. Exercise reduced p53 expression, especially when performed in the light phase. This may reflect exercise-induced increases in anti-apoptotic signals (Bcl-2), reductions in oxidative stress, and modulation of AMPK/SIRT1 pathways known to inhibit p53 activity (12, 14).

A key finding is the significant interaction between training and time of day for β-cell survival and p53 expression. This suggests that molecular pathways regulating apoptosis and metabolism are under circadian control. Previous studies show that exercise performed during phases with greater mitochondrial efficiency and antioxidant expression yields stronger benefits (11). The present results are consistent with this Chrono biological principle.

The ability of exercise to reduce p53 and enhance β-cell survival has major implications for diabetes management. Because β-cell mass declines progressively in T2DM, strategies that preserve β-cell function may delay progression, reduce medication dependence, and improve metabolic outcomes. The finding that exercise timing enhances these effects adds a new layer of clinical relevance: incorporating circadian cues may optimize therapeutic efficacy.

Sato et al. (2017) demonstrated that morning exercise enhances whole-body metabolism more effectively than evening exercise in rodents (15). Our results extend these findings by showing that pancreatic β-cell biology not just systemic metabolism is also sensitive to exercise timing. Other studies indicate that circadian disruption accelerates diabetic pathology (8, 10), reinforcing the potential importance of synchronizing lifestyle interventions with circadian rhythms.

Health Nexus
E-ISSN: 2981-2569

Strengths include the use of multiple physiological and molecular endpoints, controlled circadian training windows, and robust molecular quantification of β-cell survival and p53. Limitations include relatively small group size and use of a rodent model, which may not fully translate to humans. Inclusion of additional markers of apoptosis (e.g., BAX, Bcl-2)

5. Future Directions

Future research should examine:

- combined aerobic + resistance training in circadian phases.
- long-term effects beyond 8 weeks.
- other molecular markers (SIRT1, NF-κB, CLOCK/BMAL1).
- translational studies in human subjects.

6. Conclusion

Aerobic exercise substantially improves β-cell survival, reduces p53-mediated apoptotic stress, and enhances glycemic control in type 2 diabetic mice. Crucially, these effects are significantly modulated by circadian timing, with light-phase exercise producing superior outcomes. Incorporating circadian strategies into exercise prescriptions may enhance therapeutic efficacy for individuals with T2DM. These findings highlight the potential of Chrono-exercise as a targeted, non-pharmacological intervention to protect β-cell function and mitigate diabetes progression.

Authors' Contributions

F. Sepehrinya and M. Janbozorgi conceived the study. Methodology was designed by F. Sepehrinya and A. Taheri. Data curation and investigation were performed by A. Taheri and M. Hosseinzadeh. Formal analysis and drafting of the initial manuscript were carried out by F. Sepehrinya. Manuscript review and editing were completed by M. Janbozorgi and A. Taheri. Project supervision and administration were provided by M. Janbozorgi. All authors reviewed and approved the final version of the manuscript.

Declaration

AI-assisted tools (including large language models) were used to support English-language editing and clarity of presentation. The authors reviewed, edited, and verified all content and take full responsibility for the accuracy, integrity, and originality of the final manuscript. No AI tool was used to generate or manipulate the study data, analyses, or results.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

Acknowledgments

We hereby express our gratitude to all members of the research team and technicians at Avin Stem Gen Bio Health, whose expertise and collaboration played a crucial role in the completion of this study.

Declaration of Interest

The authors report no conflict of interest.

Funding

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

Ethics Considerations

The conduct and procedures involving animal experiments were approved by the Committee for Ethics in Animal Experiments at Shahid Chamran University (License number: IR.SCU.TEC.1404.062).

References

1. Bass J, Takahashi JS. Circadian integration of metabolism and energetics. Science. 2010;330:1349-54. [PMID: 21127246] [PMCID: PMC3756146] [DOI]
2. Boudina S, Abel ED. Diabetic cardiomyopathy, oxidative stress, and apoptosis. Circulation. 2007;115:3213-2323. [PMID: 17592090] [PMCID: PMC12210778] [DOI]
3. Zhang P, Li T, Wu X, et al. p53-mediated apoptosis in diabetic pancreatic tissue. Diabetologia. 2011;54:136-45.
4. Afzalpur ME, Taheri C, Chadorneshin H. Physical activity and oxidative stress: Bamdad Ketab; 2015. 56-70 p.
5. Ghorbanzadeh V, Mohammadi M, Mohaddes G, Darishnejad H, Chodari L. Effect of crocin and voluntary exercise on P53 protein in pancreas of type2 diabetic rats. Pharmaceutical Sciences. 2017;23(3):182-8. [DOI]
6. Safdar A, Khrapko K, Flynn JM, Saleem A, De Lisio M, Johnston AP, et al. Exercise-induced mitochondrial p53 repairs mtDNA mutations in mutator mice. Skeletal Muscle. 2015;6(1):1-18. [PMID: 26834962] [PMCID: PMC4733510] [DOI]

Health Nexus
E-ISSN: 2981-2569

7. Curran M, Drayson MT, Andrews RC, Zoppi C, Barlow JP, Solomon TP, et al. The benefits of physical exercise for the health of the pancreatic β-cell: a review of the evidence. Experimental Physiology. 2020;105(4):579-89. [PMID: 32012372] [DOI]
8. Kalsbeek A, la Fleur S, Fliers E. Circadian control of glucose metabolism. Molecular Metabolism. 2014;3:372-83. [PMID: 24944897] [PMCID: PMC4060304] [DOI]
9. Marcheva B, Ramsey KM, Buhr ED, et al. Disruption of circadian clock causes β-cell failure. Nature. 2010;466:627-31. [PMID: 20562852] [PMCID: PMC2920067] [DOI]
10. Barnea M, Madar Z, Froy O. High-fat diet and circadian clock malfunction. International Journal of Obesity. 2008;32:379-86.
11. Salto C, Arce V, et al. Timing of exercise modulates metabolic responses. Physiology & Behavior. 2017;179:1-7.
12. Fang J, Nagy L. SIRT1 and circadian regulation in metabolic disease. Trends in Endocrinology & Metabolism. 2010;21:516-23.
13. Holloszy JO. Exercise-induced increases in insulin action. Journal of Applied Physiology. 2005;99:338-43. [PMID: 16036907] [DOI]
14. Ruderman NB, Xu XJ, Nelson L, et al. AMPK and mitochondrial biology in diabetes. American Journal of Physiology - Endocrinology and Metabolism. 2010;298:E1-10. [PMID: 20103737] [PMCID: PMC2853213] [DOI]
15. Sato S, Basse AL, Schönke M, Chen S, Samad M, Altıntaş A, et al. Time of exercise specifies the impact on muscle metabolic pathways and systemic energy homeostasis. Cell Metabolism. 2019;30(1):92-110.e4. [PMID: 31006592] [DOI]
16. Chavanelle V, Boisseau N, Otero YF, Combaret L, Dardevet D, Montaurier C, et al. Effects of high-intensity interval training and moderate-intensity continuous training on glycaemic control and skeletal muscle mitochondrial function in db/db mice. Scientific Reports. 2017;7(1):1-10. [PMID: 28303003] [PMCID: PMC5427962] [DOI]
17. Ramos-Vara JA. Principles and methods of immunohistochemistry. Methods in Molecular Biology. 2011;691:83-96. [PMID: 20972748] [DOI]
18. Bustin SA, Benes V, Garson JA, Hellemans J, Huggett J, Kubista M, et al. The MIQE Guidelines: Minimum Information for Publication of Quantitative Real-Time PCR Experiments. Clinical Chemistry. 2009;55:611-22. [PMID: 19246619] [DOI]
19. Trivić T, Drid P, Obadov S, Ostojic S. Effect of endurance training on biomarkers of oxidative stress in male wrestlers. Journal of Martial Arts Anthropology. 2011;11(2):6-9.
20. Schafer MJ, White TA, Evans G, Tonne JM, Verzosa GC, Stout MB, et al. Exercise Prevents Diet-Induced Cellular Senescence in Adipose Tissue. Diabetes. 2016;65(6):1606-15. [PMID: 26983960] [PMCID: PMC4878429] [DOI]
21. Kung CP, Murphy ME. The role of the p53 tumor suppressor in metabolism and diabetes. The Journal of Endocrinology. 2016;231(2):R61. [PMID: 27613337] [PMCID: PMC5148674] [DOI]
22. Xu-Monette ZY, Medeiros LJ, Li Y, Orlowski RZ, Andreeff M, Bueso-Ramos CE, et al. Dysfunction of the TP53 tumor suppressor gene in lymphoid malignancies. Blood. 2012;119(16):3668-83. [PMID: 22275381] [PMCID: PMC3335376] [DOI]

E-ISSN: 2981-2569