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Exercise Appears to Promote Lifespan by Regulating Aging Biomarkers TAF15 and HKDC1

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Abstract

Introduction Aging is a multifaceted process at the biological level that involves cellular senescence, oxidative stress, and chronic inflammation. These components contribute to a decline in physiological function and increasedvulnerability to age-related diseases. This study investigates the influence of exercise on two key biomarkers of aging, TAF15, and HKDC1, through the comparison of their expressions between athletes and non-athletes.

Materials/Methods: Blood samples were obtained from 30 individuals, including 15 athletes and 15 non-athletes. Total RNA was extracted, after which cDNA synthesis was conducted to investigate the expression of the HKDC1 and TAF15 genes. The expression levels of both genes were subsequently determined using qRT-PCR. Indeed, theresults of HKDC1 expression presented 1.445-fold higher in athletes compared to healthy individuals, with the statistical significance level of $p = 0.007$, indicating its use in glucose metabolism and further energy balance. On the contrary, TAF15 mRNA expressed a 1.159-fold increase in athletes; however, the difference did not show statistical significance at the level of $p = 0.104$.

Conclusion: Data herein presented indicate that exercise regularly improves metabolic health and may prevent anage-related decline in metabolic health via the regulation of HKDC1 and TAF15. The current study reinforces therole of physical activity as an important therapeutic strategy in healthy aging and the prevention of age-related diseases, and further research is warranted to explain the mechanisms of these biomarkers to exercise.

Keywords: Exercise, Aging Biomarkers, TAF15, HKDC1

1. Introduction

Aging is a complex biological process wherein there is a gradual physiological decline in an organism with an increasing incidence of age-related diseases[1]. One such important process has been cellular senescence in which cells are incapable of carrying out regular cell division and further develop functional loss, promoting decline in regeneration and maintenance of tissues. Cellular senescence thus promotes aging processes using the secretion of pro-inflammatory factors[2]. Telomere shortening also contributes significantly. The telomeres are protective caps at the end of chromosomes, which, during cell division, gradually shorten until they reach a critical length and further cell division is impossible, again contributing to aging and its diseases[3]. The other important contributor is that of oxidative stress. Accumulation of ROS results in cellular damage to DNA, proteins, and lipids. This has been implicated in many age-related diseases[4]. Aging has been characterized by a low-grade chronic inflammation, recently called "inflammaging," which may

promote tissue damage and act as a risk factor for a variety of age-related diseases[5]. Furthermore, there is also animportant role of mitochondrial dysfunction in the aging process. Mitochondria are the powerhouses of the cell.

With aging, this organelle becomes less efficient in producing energy while producing more oxidative stress[6]. Changes in gene expression are among the common phenomena in aging, which can include changes in genes responsible for metabolic reactions, responses to stress, and repair mechanisms that grossly influence the process of aging[7]. Stem cell exhaustion is another important factor wherein the regenerative capacity is lowered because of the depletion and dysfunction of the stem cells themselves, hence impairing tissue repair and regeneration[8]. This results in the loss of cellular capacity for proper folding and degradation of proteins with aging, leading to the accumulation of damaged proteins and protein aggregates[9]. Epigenetic modifications refer to DNA and histone modifications independent of any actual change in DNA sequences. Indeed, these epigenetic changes have been found to influence aging and longevity[10]. This will involve metabolic changes associated with aging, including insulin resistance and a shift in lipid metabolism, which add to the development of age-related disorders like obesity and diabetes[11]. There is also extracellular matrix remodeling, where there is a change in structure and compositionthat affects tissue elasticity and function; these contribute to the age-related decline in organ systems [12].

Lifestyle factors in general, and exercise in particular, have gained increased attention in recent studies concerning their determinants on the aging process. Against the growing knowledge about the process of aging, there is a realization that regular physical activity is not for fitness maintenance alone but has an essential linkage with a range of physiological benefits that could bear great impacts on the process of aging [13]. Regular physical activity has been credited with many health benefits that go beyond weight management. Perhaps the most recognizable benefit of regular exercise is cardioprotective enhancement. Physical activities enhance heart muscles, and the person has increased blood flow, which helps maintain blood pressure and cholesterol levels. These cardiovascular benefits are indeed very relevant since heart disease remains one of the major contributors to morbidity and mortality in older adults[14]. Besides that, it has also been connected with various biological processes accompanying aging, includinginflammation, oxidative stress, and cellular repair mechanisms. Given that, physical activity can indeed influence positively those processes to contribute to the retardation of the development of age-related decline in the effort to ensure a quality life among elderly individuals.

While many molecular mechanisms could be impacted through exercise, the emphasis usually settles on the regulation of some molecules related to aging[15]. Among such molecules, there are two of the most significant molecules known as TAF15 and HKDC1 that play crucial roles in cellular processes, which are associated withaging.

While many molecular mechanisms could be impacted through exercise, the emphasis usually settles on the regulation of some molecules related to aging(15). Among such molecules, there are two of the most significant molecules known as TAF15 and HKDC1 that play crucial roles in cellular processes, which are associated withaging.

The HKDC1 gene encodes Hexokinase Domain Containing 1, a protein very important in glucose metabolism through the catalysis of glucose into glucose-6-phosphate, the first step in the pathway of glycolysis. This is very important in energy production, especially in tissues that demand energy greatly, like the brain and muscles[16]. HKDC1 is highly important during intracellular regulation of glucose levels. In the process of aging, the metabolicprocessing of glucose often becomes less efficient and might result in insulin resistance and metabolic disorders. HKDC1 mediates glucose uptake and phosphorylation at appropriate blood sugar levels to provide energy for cells[17]. Besides its role in glucose metabolism, HKDC1 supports cellular energy homeostasis by maintaining proper levels of glucose-6-phosphate. Glucose-6-phosphate is an important metabolite acting as a key player for several metabolic pathways such as glycolysis and the pentose phosphate pathway, which further contribute to supporting cellular energy homeostasis by ATP generation. Generally, with aging, there is a decline in ATP generation, leading to defective cellular functioning and senescence[18]. The gene also relates to the cellular response to oxidative stress, a condition that increases with age and has the potential to damage cellular components[19]. HKDC1 may contribute to the modulation of oxidative stress by promoting the flux of metabolites into glycolysis, which results in the generation of NADPH via the pentose phosphate pathway. NADPH is essential for the regeneration of antioxidants and thus protection from oxidative damage[16].

HKDC1, directly or indirectly, may affect inflammatory processes relevant to aging. The chronic low-grade inflammation that accompanies aging is also commonly called "inflammaging."[20]. The decrease in glucose metabolism promoted by HKDC1 modulates the production of pro-inflammatory cytokines and, subsequently, may reduce inflammation associated with aging[21.22]. Cellular senescence is a stage at which cells cease to proliferate and change function, especially in aging[23]. HKDC1 may modulate the process of senescence through metabolic flux which is key to cell survival andfunction. HKDC1 could delay senescence by facilitating energy production and reducing oxidative stress[24].

HKDC1 is also predicted to interact with several signaling pathways, such as those that govern metabolism, growth, and stress responses. This interaction could be very important for adaptation to metabolic alterations with aging and,thus, might have a strong impact on the whole aging process[24]. HKDC1 has an important role in aging due to its involvement in the processes of glucose metabolism, energy homeostasis, oxidative stress response, inflammation modulation, and cellular senescence. Understanding the molecular mechanism of HKDC1 may help uncover some great potential targets for therapy aimed at healthy aging and mitigation of age-related diseases.

The TATA-binding protein-associated factor 15, TAF15, is a part of the TAF family, which is very important in gene regulation and transcriptional control. Hence, this protein acts in various cellular activities that include RNA processing, DNA repair, and stress responses. TAF15 is well recognized for participating in the regulation of genes implicated in neuronal functions and development[25]. All through the discussion on aging, TAF15 has been implicated in several aspects of the molecular mechanisms driving this biological process. This occurs, importantly, through its presence in the regulation of gene expression. It assists in the facilitation of the assembly of transcription factors and RNA polymerase to transcribe genes necessary for cellular function[26]. Several events of aging result inan inappropriate regulation of gene expression leading to age-related decline. Thus, TAF15 helps sustain proper transcriptional activity, important for the health of the cells and longevity[27]. In addition, TAF15 plays a role in theprocessing of RNA, which is crucial during the development of premature mRNA into mature mRNA essentially an important process in the course of the expression of genes. The efficiency of RNA processing decreases in aging organisms; this might lead to the accumulation of transcripts that are wrongly processed[28]. By ensuring correct RNA processing, TAF15 partly overcomes certain aspects of aging that modulate gene expression[29]. Another important role of TAF15 is the participation in the cellular stress response, involving oxidative stress and heat shock. Often, it is at the instance of increased oxidative stress that aging can be related; this might further bring about cellular deteriorations that accelerate aging. TAF15 controls the expression of genes involved in the stress response, enhancing cellular resilience and maintaining cell viability under conditions of stress [30]. With a function in neuronal gene regulation, TAF15 has particular relevance to neurodegenerative diseases associated with aging.

Dysregulation of TAF15 has indeed been implicated in neurodegenerative conditions, lending support to the role thatthis protein could play in maintaining neuronal health and function in the aging organism[31]. TAF15 has also been implicated in the generation of RNA-protein aggregates that may be involved in cellular stress responses but whose accumulation can also contribute to age-related cellular dysfunction[32]. Understanding how TAF15 interacts with these aggregates could provide insights into the mechanisms of both aging and neurodegeneration[33].

This study aims to investigate the role of exercise in regulating TAF15 and HKDC1 in both athletes and non- athletes. By comparing these two groups, we hope to elucidate how physical activity influences the expression of these aging molecules and its subsequent impact on lifespan. Understanding these mechanisms could provide valuable insights into the potential of exercise as a therapeutic intervention for promoting healthy aging.

2. Materials and Methods

Individuals

The study population consisted of 15 athletes from clubs in Region 1 of Tehran and 15 non-athletes, selected as controls from individuals aged 20 to 35 who were free from various diseases. All participants in this study were informed about the objectives of the research project, and written consent was obtained from them. Additionally,they were provided with sufficient explanations regarding the use of the results and the

2.7. Blood collecting

Blood samples of 10 milliliters were taken from the median cephalic vein for 15 athletes and 15 participants in the control. The cubital region was cleaned properly with 70% ethanol, allowing sterilization before the blood extraction. A tourniquet was then wrapped on the upper arm to make the vein distended and more accessible. Bloodwas withdrawn with a disposable syringe fitted with a 22-gauge needle to minimize discomfort and improve blood collection.

3.8 Analysis of Gene Expression

3.8.1 Total RNAs extraction

To investigate the expression of the studied genes, the first step involved the extraction of total RNA from bloodsamples. The extracted total RNA will serve as a template for cDNA synthesis. The total RNA extraction was performed according to the user manual (Kimia Andisheh Teb company Iran- Tehran).

3.8.2Assessment of Extracted RNA Quality Using Agarose Gel Electrophoresis

In this section of the project, the quality of the extracted RNA was confirmed using the following method. To evaluate the quality of the extracted RNA, 2 µl of the RNA sample was loaded onto a 2% agarose gel. High-qualityRNA produces distinct bands corresponding to the ribosomal RNAs (rRNA) S18 and S28 on the gel. Additionally, other RNA species present in the sample appear as smears. This method was applied to all samples to ensure the quality of the extracted RNA.

3.8.3 cDNA Synthesis

The cDNA Synthesis (Pars Toos Company Tehran-Iran) contains all the necessary components for converting total RNA or mRNA into single-stranded cDNA. The reverse transcriptase (RT) enzyme used in this kit is of the H-Minustype, extracted from the Moloney Murine Leukemia Virus. The main advantage of this enzyme over other MMLV enzymes is its enhanced thermal stability. Additionally, the buffer in this kit utilizes both random hexamer primersand oligo-dT primers simultaneously to increase the efficiency of the synthesis process.

3.8.4 Primer Design

First, we accessed the Primer3Plus website at https://primer3plus.com/launch and entered the DNA/cDNA sequence we aimed to target in the provided space. We specified primer parameters such as primer length (typically 18-27 nucleotides), melting temperature (around 60 degrees Celsius is common), and GC content (usually 40-60%). We also defined the expected product size range for the PCR amplicon across the exon-exon junctions and clicked on "Primer Design." Primer3Plus analyzes the sequence and suggests optimal primer pairs. The candidate primer pairs were then validated against the genome using NCBI Primer-BLAST to confirm their specificity.

Table 1: Primer designed

	Primer Name	Sequence(5'to3')
1	HKDC1 forward	ATCCTGGCAAGCAGAGATACG
2	HKDC1 Reverse	GACGCTCTGAAATCTGCCCT
3	TAF15 Forward	GAGGATATGGCGGGTCACAG
4	TAF15 Reverse	TCTGTAGCCCCTCTCTCCAC
5	GAPDH Forward	GGAGCGAGATCCCTCCAAAAT
6	GAPDH Reverse	GGCTGTTGTCATACTTCTCATGG

3.6 Real-time PCR analysis of HKDC1 and TAF15 gene expression.

For the determination and quantification of target gene expression, qRT-PCR was performed. This technique uses the SYBR Green method, a fluorescent dye that binds non-specifically with double-stranded DNA. We will carry out qRT-PCR on the Relative Quantification method, which expresses the expression level of the gene of interest about areference gene, usually a housekeeping gene.

One of the basic needs and principles when performing Real-Time PCR is primer specificity. Therefore, the design of the primers in the preliminary step should have similar melting temperatures, appropriate lengths, and comparableGC content. After designing and synthesizing, it is necessary to validate the specificity of the RT-PCR reaction employed. This method utilizes the SYBR Green technique, which involves the use of SYBR Green fluorescent dye that non -specifically binds to double-stranded DNA. We conducted qRT-PCR using the Relative Quantification method, which compares the expression level of the target gene to that of a reference gene, typically a housekeepinggene.

One of the fundamental principles for performing Real-Time PCR is ensuring the specificity of the primers. Therefore, in the initial stage, the primers must be designed to have similar melting temperatures, appropriate lengths, and comparable GC content. After designing and synthesizing the primers, it is essential to validate theirspecificity in the RT-PCR reaction.

4.Result

4.1 Confirmation of RNA Extraction from Blood

To confirm the quality and quantity of the extracted RNA, electrophoresis was performed on a 2% agarose gel. Thepresence of three distinct bands under UV light indicated successful RNA extraction (fig1).

Using the NanoDrop device, the RNA concentrations were measured by analyzing absorbance at wavelengths of 260 and 280 nanometers. The OD260/OD280 ratio ranged from 1.8 to 2, with an average of approximately 1.9, indicating suitable RNA purity (Fig 2)

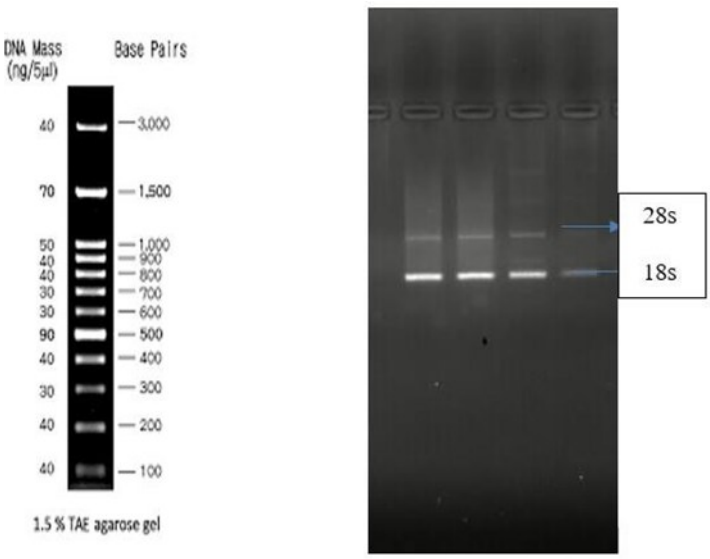

Figure 1: The presence of the 18S and 28S bands indicates the high quality of the extracted mRNA.

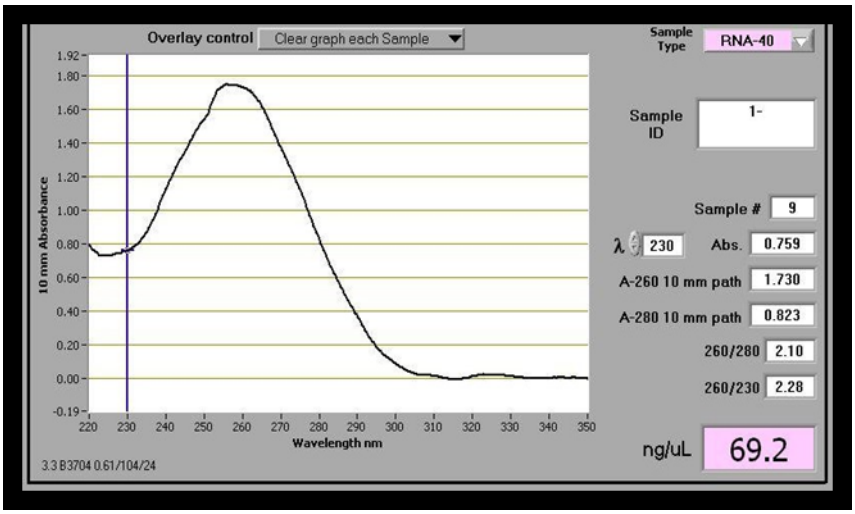

Figure 2 : the RNA concentrations

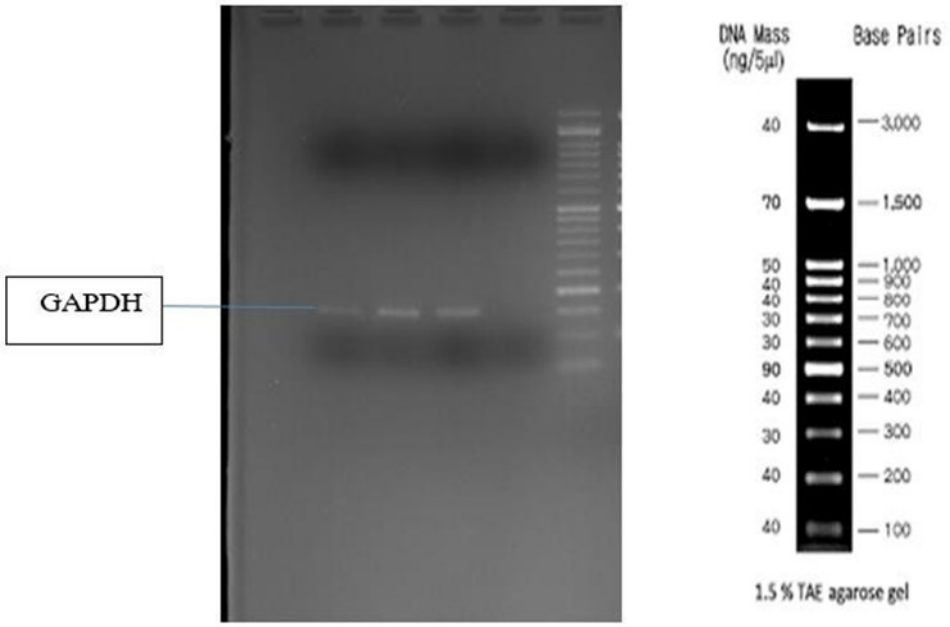

Figure 3: Results of Electrophoresis of cDNA Samples

4.2 Confirmation of Correctness of cDNA Synthesis

To check the quality of the cDNAs synthesized, all samples were subjected to PCR using the gene-specific primers for the GAPDH gene. The size of the amplified product was exactly as expected, indicating proper cDNA amplification and consequently good quality RNA and cDNA prepared. The resulting PCR products were run on a 2% agarose gel to visualize the bands that get amplified. Results are shown in Fig. In the case of the cDNA sample, results from electrophoresis clearly showed bands corresponding to the expected size of the amplified products. That means cDNA synthesis had been done and thus the quality of RNA that was used in synthesis is assured. The presence and clarity of the bands show that the cDNA is suitable for further applications in gene expression analysis (Fig 3).

4.Results

4.1 Result of BLAST Analysis for HKDC1, TAF15, and GAPDH Primers

The NCBI database search using the BLAST algorithm showed the following for HKDC1, TAF15, and GAPDH primers: The HKDC1 primers both demonstrated 100% matching with exons of the HKDC1 gene to be desired. Similarly, TAF15 primers showed a perfect match with its corresponding gene exons at 100%. Similarly, , the primersdesigned for GAPDH also showed a perfect

match with their respective exons (Fig 4). There were no primers that gave non-specific matches with other regions of the genome. Thus, the results obtained from BLAST suggest that these primers are rightly designed and selected and would be apt for the amplification intended.

Analysis of HKDC1 Gene Expression

In this analysis, the expression of the HKDC1 gene in athletes was significantly increased compared to the control group (non-athletes), with a 1.445-fold increase. This increase is statistically significant (P(H1) = 0.007). Therefore,it can be concluded that the conditions examined led to an increase in HKDC1 gene expression (Tab;2) (Fig5).

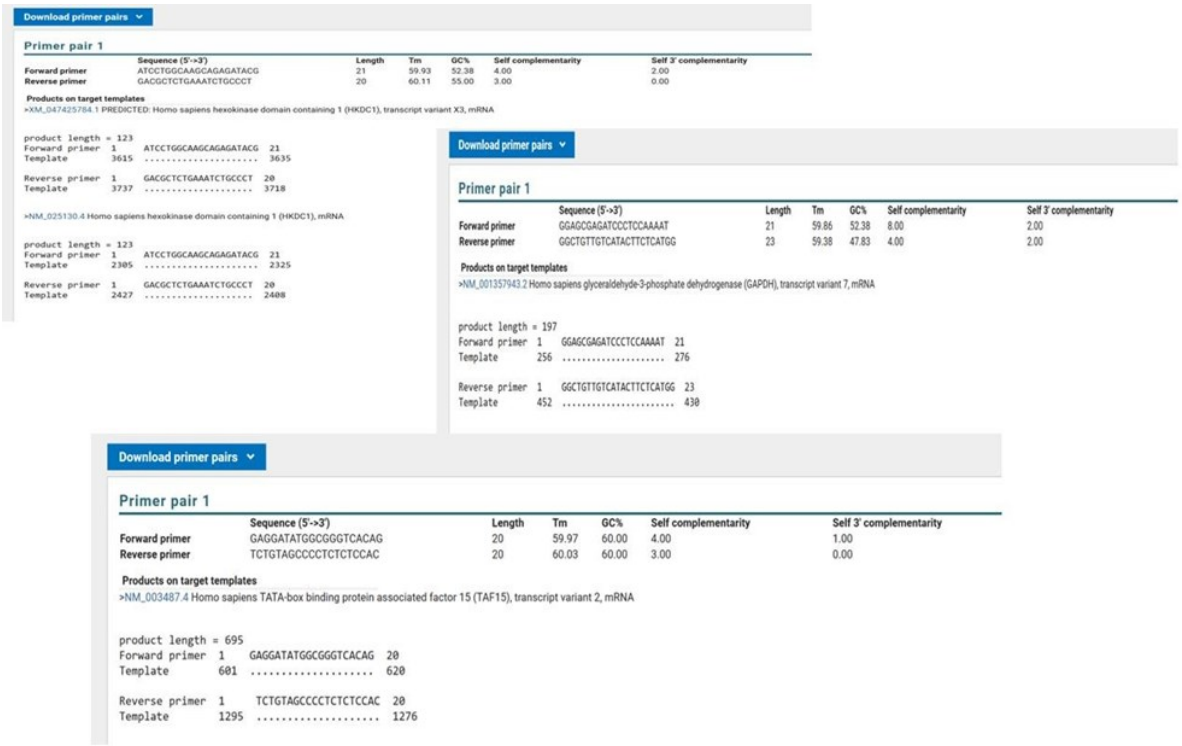

Figure 4: The result of the primer blast

Gene	Type	Reaction Efficiency	Expression	Std. Error	95% C.I.	P(H1)	Result
Control	TRG	1.0	0.976	0.754 - 1.329	0.577 - 1.640	0.741	
HKDC1	TRG	1.0	1.410	1.011 - 1.956	0.791 - 2.751	0.001	UP

Table 2: Analysis of HKDC1 Gene Expression

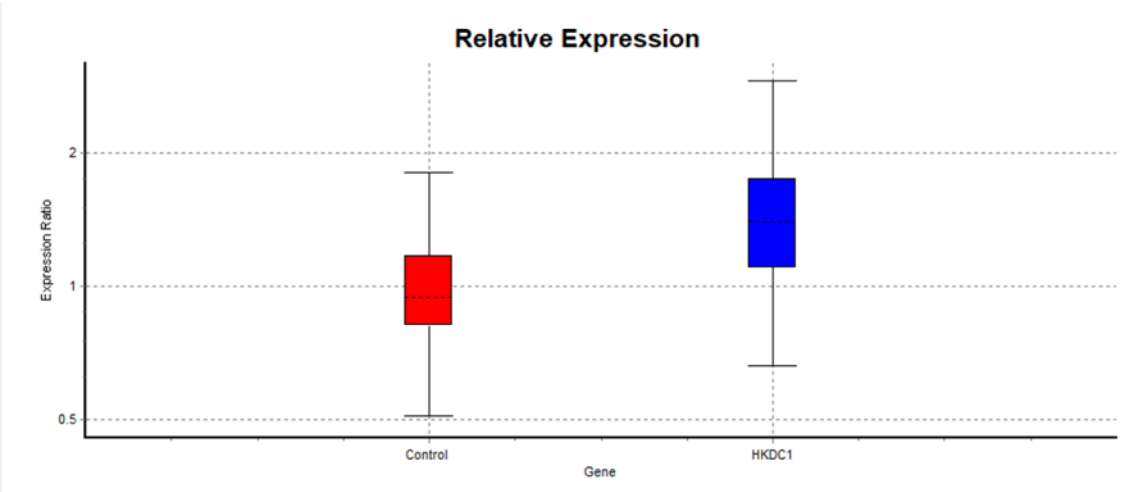

Figure 5: Analysis of HKDC1 Gene Expression

Analysis of TAF15 Gene Expression

Although the expression of the TAF15 gene in athletes showed an increase compared to the control group (non- athletes), with a 1.159-fold increase, this increase is not statistically significant (P(H1) = 0.104) (Table 3) (Fig 6).

Discussion

The findings of our research have explained in detail the influence of exercise on biomarkers of aging, particularly in genes such as TAF15 and HKDC1. Our results indicated that the levels of mRNA expression of HKDC1 were significantly higher in athletes when compared to non-athletes, thereby associating this gene with glucose metabolism and energy balance within cells. It extends the growing body of evidence supporting metabolic benefits from regular physical activity, which is greatly recognized to enhance insulin sensitivity and lower the risk of metabolic disorders related to aging.

Considering its involvement in regulating glucose levels and in the response to oxidative stress, HKDC1 appears quite important in cellular function and longevity[34]. HKDC1 seems to facilitate energy production by promoting glucose uptake and phosphorylation, a key process for high-energy tissues such as muscles and the brain[35].

Gene	Type	Reaction Efficiency	Expression	Std. Error	95% C.I.	P(H1)	Result
Control	TRG	1.0	0.976	0.754 - 1.329	0.577 - 1.640	0.724	
TAF15	TRG	1.0	1.131	0.973 - 1.283	0.909 - 1.703	0.002	UP

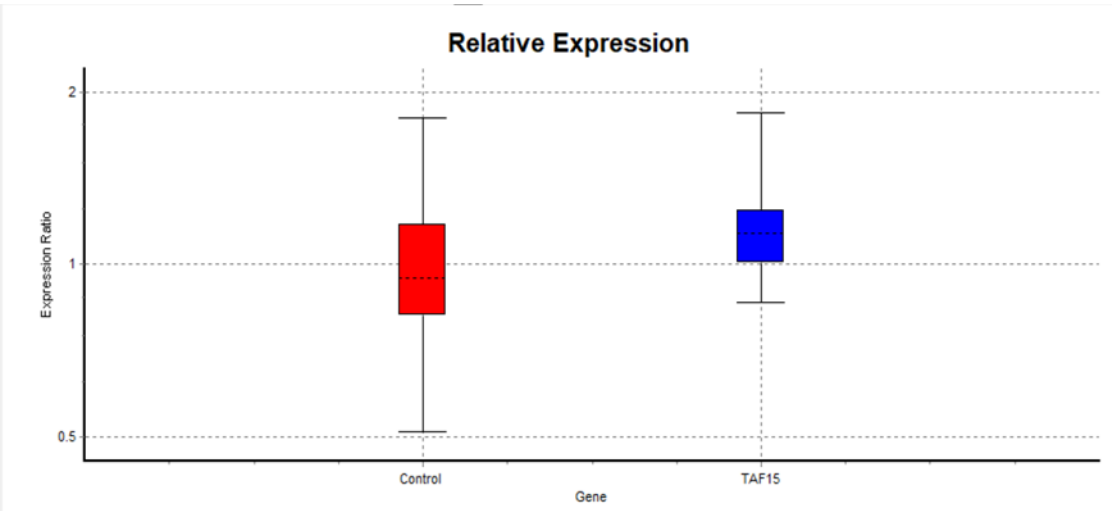

Figure 6: Analysis of Taf15 Gene Expression

Regular exercise would appear to improve metabolic efficiency, counteracting the declines associated with aging, asthe increase in the expression of HKDC1 was quite significant among athletes[24,36].

On the other hand, while the level of TAF15 expression was indeed higher in athletes compared with non-athletes, the observed increase was not statistically significant. With TAF15 implicated in regulating gene expression, RNA processing, and cellular responses to stress, one would imagine that this gene might well have a critical role in sustaining cellular health and function. Especially considering the involvement in transcriptional control and stress response mechanisms, it is plausible to assume that TAF15 might be crucial in cellular resistance during conditions of aging[37]. On the other hand, these results could suggest that the impact of exercise on TAF15 expression is moresubtle and could take an even longer or much more extended intervention to exhibit sharper differences.

Our findings have implications beyond individual biomarkers. The interplay between exercise, HKDC1, and TAF15points to a much broader molecular landscape of aging. Modulation of these markers by exercise may have collective impacts on processes such as oxidative stress, inflammation, and cellular senescence. Such interconnectedness would suggest that increasing physical activity might play a pivotal role in the promotion of healthy aging and the prevention of age-related diseases[38].

The mechanism of exercise, which regulates such biomarkers of aging as HKDC1 and TAF15, may be instructive for therapeutic strategies against metabolic and neurodegenerative diseases[39]. These results push the inclusion ofmore intense physical activity as an integral part of healthy aging in tune with public health recommendations emphasizing regular exercise as a key component of healthy living and longevity[40].

The investigation of the expression of HKDC1 and TAF15 for the regulating pathways involved is beyond the scopeof the present study and shall be the target of future studies. Longitudinal studies on the effects induced by differenttypes of exercise on these biomarkers can provide further insights into optimal exercise to promote healthspan and longevity. Further investigation of the exercise effects on other candidate genes related to aging and pathways may contribute to a better understanding of the molecular underpinnings that determine the beneficial effect of physical activity.

Conclusion

The current study pointed out the major influence of regular exercise on the expression of two key aging biomarkers, HKDC1 and TAF15. Our findings indicate that HKDC1 level in athletes is remarkably higher compared with non- athletes, underlining the positive role of physical activity in improving glucose metabolism and cellular energy homeostasis. Although athletes had higher TAF15 expression, the difference was not statistically significant, thus this relation to exercise and aging may require further investigation. Modulation of these biomarkers reflects the complex interaction of lifestyle factors with biological aging processes. Regular physical activity supports metabolic health and may also protect against age-related declines in cellular function and resilience. These findings underscore the inclusion of exercise in daily life as a key strategy in healthy aging and the prevention of age-related diseases. It would be worth it if further research could elucidate the mechanisms that regulate the expressions of HKDC1 and TAF15 by different exercise modalities. The deeper the understanding of such molecular processes, the better harnessing of the therapeutic potential of physical activity for healthspan and longevity extension.

References

1. *Li Z, Zhang Z, Ren Y, Wang Y, Fang J, Yue H, et al. Aging and age-related diseases: frommechanisms to therapeutic strategies. Biogerontology. 2021 Apr 27;22 (2):165–87.*
2. *Huang W, Hickson LJ, Eirin A, Kirkland JL, Lerman LO. Cellular senescence: the good, the bad and the unknown. Nat Rev Nephrol. 2022 Oct;18(10):611–27.*
3. *Muraki K, Nyhan K, Han L, Murnane JP. Mechanisms of telomere loss and their consequences for chromosome instability. Front Oncol. 2012;2.*
4. *Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, et al. Oxidative stress, aging, anddiseases. Clin Interv Aging. 2018 Apr;Volume 13:757–72.*
5. *Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018 Sep 31;15(9):505–22.*
6. *Chistiakov DA, Sobenin IA, Revin V V., Orekhov AN, Bobryshev Y V. Mitochondrial Aging and Age-Related Dysfunction of Mitochondria. Biomed Res Int. 2014;2014:1–7.*

7. Zapater JL, Lednovich KR, Khan MdW, Pusec CM, Lay den BT. Hexokinase domain-containingprotein-1 in metabolic diseases and beyond. Trends in Endocrinology & Metabolism. 2022 Jan;33(1):72–84.

8. Liu P, Luo Y, Wu H, Han Y, Wang S, Liu R, et al. HKDC1 functions as a glucose sensor and promotes metabolic adaptation and cancer growth via interaction with PHB2. Cell Death Differ. 2024 Oct 7;

9. Liu P, Luo Y, Wu H, Han Y, Wang S, Liu R, et al. HKDC1 functions as a glucose sensor and promotes metabolic adaptation and cancer growth via interaction with PHB2. Cell Death Differ. 2024 Oct 7;

10. Klein JA, Ackerman SL. Oxidative stress, cell cycle, and neurodegeneration. Journal of ClinicalInvestigation. 2003 Mar 15;111(6):785–93.

11. Baechle JJ, Chen N, Makhijani P, Winer S, Furman D, Winer DA. Chronic inflammation and thehallmarks of aging. Mol Metab. 2023 Aug;74:101755.

12. Shi J, Fan J, Su Q, Yang Z. Cytokines and Abnormal Glucose and Lipid Metabolism. FrontEndocrinol (Lausanne). 2019 Oct 30;10.

13. Pusec CM, De Jesus A, Khan MW, Terry AR, Ludvik AE, Xu K, et al. Hepatic HKDC1 ExpressionContributes to Liver Metabolism. Endocrinology. 2019 Feb 1;160(2):313–30.

14. Huang W, Hickson LJ, Eirin A, Kirkland JL, Lerman LO. Cellular senescence: the good, the bad andthe unknown. Nat Rev Nephrol. 2022 Oct 3;18(10):611–27.

15. Cui M, Yamano K, Yamamoto K, Yamamoto-Imoto H, Minami S, Yamamoto T, et al. HKDC1, a target of TFEB, is essential to maintain both mitochondrial and lysosomal homeostasis, preventingcellular senescence. Proceedings of the National Academy of Sciences. 2024 Jan 9;121(2).

16. Van Roon-Mom WMC, Reid SJ, Faull RLM, Snell RG. TATA-binding protein in neurodegenerativedisease. Neuroscience. 2005;133(4):863–72.

17. Liu P, Luo Y, Wu H, Han Y, Wang S, Liu R, et al. HKDC1 functions as a glucose sensor and promotes metabolic adaptation and cancer growth via interaction with PHB2. Cell Death Differ. 2024 Oct 7;

18. Liu P, Luo Y, Wu H, Han Y, Wang S, Liu R, et al. HKDC1 functions as a glucose sensor and promotes metabolic adaptation and cancer growth via interaction with PHB2. Cell Death Differ. 2024 Oct 7;

19. Klein JA, Ackerman SL. Oxidative stress, cell cycle, and neurodegeneration. Journal of Clinical Investigation. 2003 Mar 15;111(6):785–93.

20. Baechle JJ, Chen N, Makhijani P, Winer S, Furman D, Winer DA. Chronic inflammation and the hallmarks of aging. Mol Metab. 2023 Aug;74:101755.

21. Shi J, Fan J, Su Q, Yang Z. Cytokines and Abnormal Glucose and Lipid Metabolism. Front Endocrinol (Lausanne). 2019 Oct 30;10.

22. Pusec CM, De Jesus A, Khan MW, Terry AR, Ludvik AE, Xu K, et al. Hepatic HKDC1 ExpressionContributes to Liver Metabolism. Endocrinology. 2019 Feb 1;160 (2):313–30.

23. Huang W, Hickson LJ, Eirin A, Kirkland JL, Lerman LO. Cellular senescence: the good, the bad and the unknown. Nat Rev Nephrol. 2022 Oct 3;18(10):611–27.

24. Cui M, Yamano K, Yamamoto K, Yamamoto-Imoto H, Minami S, Yamamoto T, et al. HKDC1, a target of TFEB, is essential to maintain both mitochondrial and lysosomal homeostasis, preventing cellular senescence. Proceedings of the National Academy of Sciences. 2024 Jan 9;121(2).

25. Van Roon-Mom WMC, Reid SJ, Faull RLM, Snell RG. TATA-binding protein in neurodegenerative disease. Neuroscience. 2005;133(4):863–72.

26. Tang L, Guo C, Li X, Zhang B, Huang L. TAF15 promotes cell proliferation, migration and invasion ofgastric cancer via activation of the RAF1/MEK/ERK signalling pathway. Sci Rep. 2023 Apr 10;13(1):5846.

27. He Y, Liu B, Yang F, Yang Q, Xu B, Liu L, et al. <scp>TAF15</scp> downregulation contributes to the benefits of physical training on dendritic spines and working memory in aged mice. Aging Cell. 2024 Sep 14;23(9).

28. Cookson MR. Aging—RNA in development and disease. WIREs RNA. 2012 Jan 6;3(1):133–43.

29. He Y, Liu B, Yang F, Yang Q, Xu B, Liu L, et al. <scp>TAF15</scp> downregulation contributes to the benefits of physical training on dendritic spines and working memory in aged mice. Aging Cell. 2024 Sep 14;23(9).

30. Singh AK, Kapoor V, Thotala D, Hallahan DE. TAF15 contributes to the radiation-inducible stressresponse in cancer. Oncotarget. 2020 Jul 7;11(27):2647–59.

31. Tetter S, Arseni D, Murzin AG, Buhidma Y, Peak-Chew SY, Garringer HJ, et al. TAF15 amyloidfilaments in frontotemporal lobar degeneration. Nature. 2024 Jan 11;625(7994):345–51.

32. DeJong CS, Dichmann DS, Exner CRT, Xu Y, Harland RM. The atypical RNA-binding protein Taf15regulates dorsoanterior neural development through diverse mechanisms in Xenopus tropicalis.Development. 2021 Aug 1;148(15).

33. Svetoni F, Frisone P, Paronetto MP. Role of FET proteins in neurodegenerative disorders. RNA Biol.2016 Nov 1;13(11):1089–102.

34. Cui M, Yamano K, Yamamoto K, Yamamoto-Imoto H, Minami S, Yamamoto T, et al. HKDC1, a target of TFEB, is essential to maintain both mitochondrial and lysosomal homeostasis, preventingcellular senescence. Proceedings of the National Academy of Sciences. 2024 Jan 9;121(2).

35. Khan MdW, Ding X, Cotler SJ, Clarke M, Layden BT. Studies on the Tissue Localization of HKDC1, aPutative Novel Fifth Hexokinase, in Humans. Journal of Histochemistry & Cytochemistry. 2018 May 5;66(5):385–92.

36. Grevendonk L, Connell NJ, McCrum C, Fealy CE, Bilet L, Bruls YMH, et al. Impact of aging and

37. exercise on skeletal muscle mitochondrial capacity, energy metabolism, and physical function. NatCommun. 2021 Aug 6;12(1):4773.

38. Nickerson JA, Momen-Heravi F. Long non-coding RNAs: roles in cellular stress responses andepigenetic mechanisms regulating chromatin. Nucleus. 2024 Dec 31;15 (1).

39. Izquierdo M, Merchant RA, Morley JE, Anker SD, Aprahamian I, Arai H, et al. International ExerciseRecommendations in Older Adults (ICFSR): Expert Consensus Guidelines. J Nutr Health Aging. 2021 Jul;25(7):824–53.

40. Sujkowski A, Hong L, Wessells RJ, Todi S V. The protective role of exercise against age-relatedneurodegeneration. Ageing Res Rev. 2022 Feb;74:101543.

41. Reimers CD, Knapp G, Reimers AK. Does Physical Activity Increase Life Expectancy? A Review ofthe Literature. J Aging Res. 2012;2012:1–9.