Research Article

The effect of high intensity interval training and Nano selenium supplementation on the expression of IL-10 and IL-12 genes in testicular tissue in rat under the use of dexamethasone

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Abstract

Interval training and selenium is an effective way to strengthen the immune system. The purpose of this research was to investigate the effect of High intensity interval training and Nano selenium supplementation on the expression of IL-10 and IL-12 genes in the testicular tissue of rat under dexamethasone administration. 40 Wistar rats aged 10 weeks were randomly divided into 5 groups of 8 (healthy, dexamethasone induced (patient), High intensity interval training + patient, Nano selenium supplement + patient, High intensity interval training + Nano selenium supplement+ patient). the exercise training program consisted of 5-12 repetitions of 1-minute running on the rodent treadmill with an intensity of 24-30 m/min, equivalent to 75-100% of maximal oxygen consumption, with active rest intervals of 75 seconds. These trainings were performed six days a week for four weeks. The prepared selenium nanoparticle solution, 100 mg in 250 nm size, was given to rat by gavage every other day. One-way analysis of variance was used to determine the difference in variables between groups at a significant level ($P<0.05$). All statistical calculations were done using SPSS version 25 software. The obtained results showed that interval training and Nano selenium supplementation led to a significant decrease in IL-10 ($P<0.05$). Also, IL-12 gene expression increased significantly along with interval training and Nano selenium supplementation ($P<0.05$). According to the current research, it seems that High intensity interval training and Nano selenium supplementation lead to improved immune function and possibly the ability to develop antioxidant defenses and reduce cellular oxidative stress.

Key Words: **Dexamethasone, High intensity interval training, Nano selenium, IL-10, IL-12**

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Introduction

Selenium is an important trace mineral that has many essential roles at the cellular and organismal levels in animal and human health. It is evident from the past studies that selenium is essentially required for spermatogenesis and male fertility, possibly due to its critical role in modulating antioxidant defense mechanisms and other essential biological pathways (Qazi et al., 2019). Selenium is a component of antioxidant enzymes, including glutathione peroxidase, which plays a role in neutralizing free radicals and relieving oxidative stress (Soleimani Ghaleh et al., 2022). Among the parts of the reproductive system, the testis has the highest concentration of selenium, which is even higher than the liver. Decreasing selenium concentration probably makes the testicular tissue more vulnerable (Ramírez-Acosta et al., 2022).

The speed of mitosis and different stages of meiosis in the seminiferous tubules make the germ cells susceptible to the local inhibition effects of free radicals. Selenium as an antioxidant is found in large quantities in seafood, liver and grains (Nakagawa et al., 2017). Dexamethasone is a synthetic corticosteroid (a glucocorticoid) used to treat a variety of conditions. It acts as an anti-allergic and immunosuppressive agent (Noreen et al., 2021). During the initial acute inflammatory phase, it is involved in reducing the synthesis of vasoactive elements and is therefore an effective anti-inflammatory. Dexamethasone and other glucocorticoids are widely used to treat autoimmune diseases, allergic responses, and protection against transplant rejection.

Moreover, glucocorticoids bind to specific DNA sequences which are accessed by translocation through cell receptors (Coutinho & Chapman, 2011). Dexamethasone affects testicular homeostasis, induces apoptosis in testicular germ cells, and causes defects in spermatogenesis such as histopathological and morphometric changes, changes in sperm count, and puberty arrest in rat. Administration of dexamethasone decreases the activity of antioxidant enzymes, plasma melatonin level and also melatonin receptor expression,

which subsequently increases lipid peroxidation and changes the histopathology of the testis, which may result in increased apoptosis of germ cells. Inhibition of antioxidant capacity and increase of reactive oxygen species in reproductive cells causes oxidative damage and therefore plays a key role in the pathogenesis of male infertility (Orazizadeh et al., 2010).

IL-10 is an immunosuppressive cytokine produced by monocytes, macrophages, activated B cells, and Th2 cells, and plays a role in regulating immune responses and tumorigenesis (Iyer & Cheng, 2012; Riyahi Malayeri et al., 2019). Furthermore, IL-10 plays a key role in mediating and suppressing inflammatory responses, and IL-10 deficiency increases inflammatory responses. As a product of Th2 polarized CD4+ T cells, IL-10 inhibits CD4+ T cell proliferation and Th1 helper cell cytokine secretion and induces CD8+ T cell cytotoxicity (Jankovic, Kugler, & Sher, 2010; Kalhor et al., 2020). In general, IL-10 plays a key protective role in many autoimmune responses and diseases (Farazandeh Nia et al., 2018). Interleukin-12 is an immunoregulatory cytokine that can activate NK cells, generate lymphokine-activated killer cells, and induce interferon γ production and T cell proliferation. Interleukin-12 is a heterodimeric proinflammatory cytokine that promotes the differentiation of Th 1 cells and provides a link between innate resistance and adaptive immunity (Liu et al., 2005). Dendritic cells and phagocytes produce IL-12 in response to pathogens during infection (Hamza et al., 2010). IL-12 has strong anti-tumor activity and has therapeutic application in cancer patients. Furthermore, IL-12 has been shown to inhibit angiogenesis which is important during interval training. IL12 is basically one of the heterodimeric pro-inflammatory cytokines generally sent by dendritic cells and phagocytes and stimulates the production of interferon-γ, which is important for the isolation of Th1 cells and links between innate opposition and versatile invulnerability (Tugues et al., 2015).

High-intensity interval training (HIIT) is a modern type of aerobic training defined as repeated attempts to perform high-intensity training with interval rest or low-intensity activity as recovery periods (Malayeri et al., 2014; Riyahi Malayeri et al., 2019). Recently, HIIT has been reported to have significant protective effects on various tissues compared to conventional endurance training (Riyahi Malayeri & Saei, 2019). Also, the findings of Maleki and Tartibian showed that 24 weeks of HIIT led to a significant improvement in the indicators of oxidative stress and inflammation of seminal fluid, parameters of seminal fluid and sperm DNA integrity in infertile men. In recent decades, it has been found that reactive oxygen species plays a role in causing most types of male infertility, and the cause is excessive production of reactive oxygen species or reduction in the capacity of the antioxidant system of the reproductive system and sperm. Besides, a number of studies using markers of oxidative stress have investigated the effect of interval training on markers of male reproductive performance in the testes.

Although studies in this field are still scarce, they indicate that interval training plays an important role in improving markers of male reproductive performance in healthy and infertile individuals, particularly by reducing inflammatory markers and oxidative stress (Hajizadeh Maleki & Tartibian, 2020). In fact, homeostasis in the cell and especially at the level of the organism, the balance between the formation of reactive oxygen species and reactive nitrogen species and antioxidant reactions is crucial to maintain the appropriate level of reactive oxygen species and minimize their specific reactions with biological molecules (Pizzino et al., 2017). Considering the effects of interval training and selenium on immune function and oxidative stress, the aim of this study was to investigate the effect of High intensity interval training and Nano selenium supplementation on the expression of IL-10 and IL-12 genes in the testicular tissue of mice under dexamethasone administration.

Materials and Methods

Animals

The present study adopted a quasi-experimental design with a post-test conducted on five groups. In this study, 40 Wistar rats aged 10 weeks were randomly divided into 5 groups of 8: healthy, dexamethasone induced (patient), High intensity interval training + patient, Nano selenium supplement + patient, High intensity interval training + Nano selenium supplement+ patient. The rats were kept in the animal laboratory of the Physiology Department under controlled conditions of light (12 hours of light and 12 hours of darkness, lighting starts at 6 in the morning and off at 6 in the evening), temperature (22 ± 3 C), and humidity (about 45%). Three to five rats were kept in Plexiglas cages with a mesh door and measuring 25 x 27 x 43 cm in such a way that they had free access to water and standard food.

After three days of familiarization with the environment, the animals were familiarized with the treadmill and how to run on it for 10 minutes daily and five times a week for one week. After 48 hours of rest from the last familiarization session, mice were taken to measure the maximum speed of the inhibitory test. For the test to determine the maximum speed, the rats were fasted for four hours before the test, and the test was performed between 9 and 11 in the morning. The animals performed the warm-up program at a speed of 5 meters per minute for 5 minutes and then started the test at a speed of 9 meters per minute. In the continuation of the test, the speed of the conveyor belt increased by 2 meters per minute every 2 minutes until the animal

Table 1. Exercise training protocol

	Repetitions × Training Duration (Training Intensity) Light Activity Duration × (Light Activity Intensity)
The First week	5×1min(24m/min) ×75sec (5m/min)
The Second week	8×1min(24m/min) ×75sec (5m/min)
The third week	10×1min(28m/min) ×75sec (5m/min)
The Forth week	10×1min(30m/min) ×75sec (5m/min)

reached a stop. The criterion of animal retardation was the inability to return to running on the treadmill within 10 seconds (Mohammadi et al., 2022).

How dexamethasone weakens the immune system

To weaken the immune system of rat, the amount of 0.4 mg/kg/d, dexamethasone (manufactured by Osveh Company, Iran) was injected intraperitoneal for three days (Dehghani et al., 2021).

Consumption of selenium nanoparticles

To prepare selenium nanoparticles, in brief, 2.5 mM selenium dioxide solution was prepared and added to 2.5 mM ascorbic acid solution while mixing. The obtained mixture was centrifuged and washed using filter paper. The prepared selenium nanoparticle solution, 100 mg in 250 nm size, was injected into rat by gavage every other day (Moayeri et al., 2018).

Exercise training protocol

Interval training including running on the rodent treadmill at a speed of 24 to 30 meters per minute, equivalent to 75 to 100% of the maximum oxygen consumption, was performed six days a week for four weeks (Arabzadeh et al., 2022; Hedayati et al., 2018; Mirsepasi et al., 2019) which is shown in Table 1 of the training protocol.

Histology and Biochemical Analysis of Variables

At the end of the training and supplement interventions, the rats were taken to the laboratory and sacrificed, and the IL-10 and IL-12 genes tissue samples were first designed for primer design, and then total RNA was extracted from the tissues and converted into cDNA. Then, the cDNA was amplified by PCR and analyzed for the expression of the mentioned genes. This technique had 4 basic steps: 1) Total RNA was extracted from the cells collected in each group; 2) It was converted into cDNA using reverse transcription enzyme; 3) The resulting cDNA was treated with DNase I enzyme to remove genomic DNA; and 4) It was amplified by Real time PCR method. For molecular investigations at the level of gene expression, first, RNA extraction from tissues in all investigated groups was performed according to the manufacturer's protocol (Qiagen, Germany). Then, comparative ΔΔCT method was used to quantify IL-10 and IL-12 mRNA expression.

Statistical analysis

After collecting the required information, it was analyzed by SPSS 25 statistical software at a significance level of $p>0.05$. One-way analysis of variance test was used to compare the means and Bonferroni's post hoc test was used in the five groups.

Results

In order to investigate the effect of interval training and Nano selenium consumption on IL-10 gene expression in dexamethasone-induced rats, a one-way analysis of variance was performed. The results obtained from the one-way analysis of variance test with a significance level less than 0.05 showed that there is a significant difference between the IL-10 gene variable in the five research groups (P=0.000). As a result, it can be stated that HIIT training and Nano selenium supplementation have a significant effect on IL-10 gene expression in rat testicular tissue cells (Figure 1).

The results of the Bonferroni post hoc test showed that IL-10 levels increased significantly in the dexamethasone, Nano selenium supplement and interval training groups compared to the healthy group. Also, the values of IL-10 gene expression in the testicular tissue in the groups of interval training and the combination of selenium supplement and interval training were significantly lower than in the dexamethasone group.

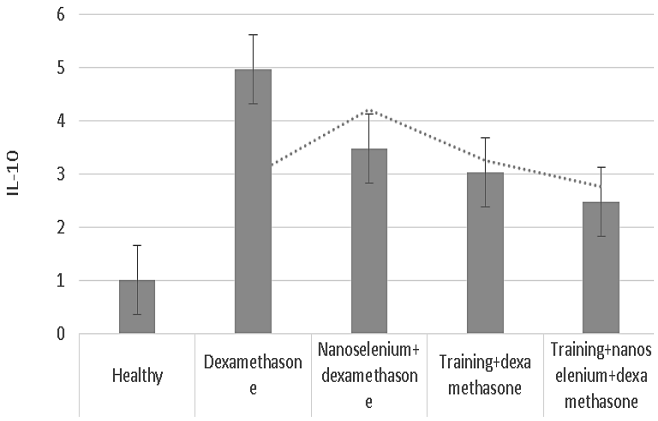

Figure 1. IL-10 gene expression levels in five research group. Data were shows as means ± SD.

Table 2. Sequence of primers

	Genes Name	Primer Sequences
1	Interleukin 10 (IL-10)	Forward: CTGCTCTTACTGGCTGGAGT
		Reverse: TGGGAAGTGGGTGCAGTTAT
2	Interleukin 12 (IL-12)	Forward: TGTTGTAGAGGTGGACTGGC
		Reverse: ACAGTGATGGTCAGGGTCTT
3	GAPDH	Forward: CAAGTTCAAGGGCACAGTCA
		Reverse: CCCCATTTGATGTTAGCGGG

The results obtained from the one-way analysis of variance with a significance level of less than 0.05 showed that there is a significant difference between the IL-12 gene expression in the five research groups (P=0.000). It was revealed that interval training and Nano selenium supplementation have a significant effect on IL-12 gene expression in rat testicular tissue cells, and this effect was different in different groups (Figure 2).

The results of the Bonferroni post hoc test showed that IL-12 levels in the dexamethasone, Nano selenium supplement, and interval training groups had a significant decrease compared to the healthy group, but this decrease was not significant in the combined Nano selenium supplement and interval training group. Also, the values of IL-12 gene expression of testicular tissue in the groups of interval training and the combination of selenium supplement and interval training were significantly higher than the dexamethasone group. The results show a significant increase in IL-12 gene values in the group of Nano selenium supplement and interval training compared to the interval training group.

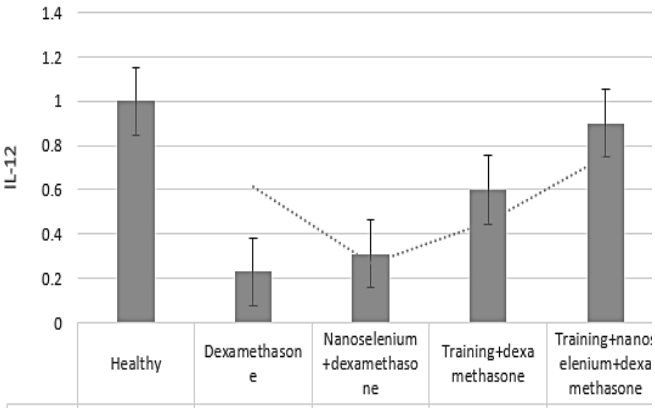

Figure 2. IL-12 gene expression levels in five research group. Data were shows as means ± SD.

Discussion

The finding of the present research showed the increase in IL-10 gene expression after dexamethasone injection, which was significantly higher in the dexamethasone, dexamethasone + Nano selenium and dexamethasone + interval training groups than the healthy control group. Also, the expression values of this anti-inflammatory gene in dexamethasone + interval training and dexamethasone + interval training + Nano selenium groups significantly reduced compared to the dexamethasone group. In agreement with the current research, Nasan et al. (2021) investigated the effect of onion extract on the testicles of rats under the drug dexamethasone. The levels of IL-10 and IL-12, which decreased in the dexamethasone group, were normalized by the consumption of onion extract. Dexamethasone decreased GSH, total antioxidant activity and testosterone levels, while treat with onion extract normalized these levels. MDA increased in the dexamethasone group but appeared normal in the experimental group. Dexamethasone was shown to decrease IL-10 and IL-2 gene expression. Conversely, IL-1β and caspase-3 gene expression was regulated by dexamethasone and normalized in the group receiving the treatment (Nassan et al., 2021).

Histopathological analysis showed that dexamethasone causes atrophy of spermatogenic tubules and degeneration into spermatocytes while immune-histochemical analysis showed overexpression of caspase-9 and inhibition of Bcl-2 expression in dexamethasone group. It seems that the consumption of onion extract, due to the presence of quercetin, increases the antioxidant capacity and reduces inflammation in the testicles, and this has been shown by reducing the number of inflammatory interleukins (Nassan et al., 2021). In fact, with the injection of glucocorticoids, their side effects increase, one of which is the creation of oxidative stress conditions in cells (Ramamoorthy & Cidlowski, 2016). The main reason for using dexamethasone is to suppress the body's immune system to reduce inflammatory responses, and this will not improve the physiological conditions of the body to reduce chronic inflammation. On the other hand, dexamethasone injection disrupts the antioxidant balance of testicular cells, which leads to side effects such as a decrease in testosterone production, a decrease in the number and quality of sperms, and in some cases, this loss of antioxidant balance causes the destruction of sperms. Therefore, the increased expression of the interleukin-10 gene seems to be a response to the pathological conditions created by dexamethasone to control systemic inflammation (Dutta et al., 2021).

Contrary to our research, Mohammadpour and Mohammadeini (2021), using prednisolone injection and selenium consumption in rat, did not observe proper function in sperms and the weight of the testicles reduced, which can be attributed to the anti-inflammatory drug different from the present study. In the examination of the average number of sperms in the groups treated with prednisolone and sodium selenite, it was shown that prednisolone in concentrations of 1.5 and 2.5 mg/kg can reduce the number of sperm production, which is significantly different compared to the control group and other groups. Finally, selenium is one of the most essential elements in testicular tissue

and is basically required for spermatogenesis and male fertility. It can also act as a protective barrier in preventing the harmful effects of corticosteroids. Also, the duration of drug use in their study was 2 times as much as that of our study, which can increase inflammation more. It can be stated that the duration of treatment with anti-inflammatory drugs and the type of drug used are the most important factors in the spread of oxidative stress (Mohammadpour & Mohammadeini, 2021), which were high in the research of these researchers. However, in the present study, the duration of dexamethasone consumption was not high, and on the other hand, in addition to supplementing interval training activity, it also has its antioxidant effects. The increase in IL-10 gene expression in the groups with dexamethasone compared to the control group indicates that despite the anti-inflammatory nature of dexamethasone, the cellular conditions and oxidative stress in the testicles increase and the response of immune cells increases IL-10 secretion. The important point is that interventions such as antioxidant substances such as selenium and regular interval training activity have been able to reduce some of this pathological cell stress in the testicles so that we have a lower response from IL-10.

Conclusion

The findings showed that interval training alone or with selenium supplementation has been able to prevent a significant increase in IL-10 compared to dexamethasone, but selenium supplementation alone has reduced IL-10 gene expression levels. These findings indicate that the body's inherent antioxidant defenses with physiological interventions such as high intensity interval training are much stronger and greater than the antioxidant properties of substances such as selenium. Nevertheless, the combination of interval training with the use of supplements basically had a greater antioxidant response than each of these interventions alone, although this effect was not significant compared to the interval training group and the supplement group alone. In agreement with the present study, Davodi et al. (2021) caused testicular inflammation in rat by taking the drug doxorubicin. Then, they started to intervene by prescribing intense interval training and consuming crocin. Their results showed that training and crocin supplementation simultaneously have a greater effect on increasing the antioxidant capacity of testicular cells. The results of the study showed that doxorubicin caused oxidative stress in the testicular tissue by decreasing the level of GPX and TAC and increasing the level of PC. The increase in the antioxidant level in the crocin and training group appears to be dose-dependent. The simultaneous use of supplements and interval training can better manage pathological conditions with a higher development of antioxidant capacity and have better effects on the number and quality of sperm as well as their performance in the long run (Davoodi et al., 2021).

Generally, intense interval training activity in healthy people and in sick people can reduce inflammatory responses by improving antioxidant conditions and increasing the body's total antioxidant capacity, which reduces the need for IL-10 secretion in cells (Steen et al., 2020). On the other hand, in sick people or people with inflamed and obese bodies, due to increased oxidative stress, systemic inflammation increases, which faces IL-10 responses. Therefore, in pathological and inflammatory conditions, the expression of IL-10 gene develops, and high intensity interval training and Nano selenium supplementation can significantly improve conditions compared to the initial inflammatory state.

Interleukin 10 is a strong anti-inflammatory and one of its action pathways is the suppression of interleukin 12. That is, if the inflammatory condition of the cell is established and the antioxidant capacity of the cell decreases or the oxidative stress increases (Taherkhani et al., 2020), interleukin 10 will increase and will perform its action by suppressing and reducing interleukin 12. So it is natural that when IL-10 increases, IL-12 decreases and vice versa!

Despite its anti-inflammatory and immunosuppressive effects, the use of dexamethasone increases the oxidative stress of the testicles and creates a pathological condition and an antioxidant imbalance in the testicular cells. The body's immune cells give a faster and stronger inflammatory response to these conditions, which leads to an increase in IL-10 gene expression in testicular cells. With the presence of IL-10, the expression of interleukin 12 gene decreases because IL-10 is an anti-inflammatory factor (Prihatno et al., 2020). In the current research, in the intervention groups that received dexamethasone injection, IL-12 levels decreased due to the increase of IL-10, and this shows that the condition is still inflammatory compared to the health condition after dexamethasone injection. Now, once the conditions are removed from the pathological state, the IL-12 levels also return to their healthy levels, in a way that in the intervention group of interval training and intake Nano selenium supplements at the same time, the antioxidant capacity has improved and the IL-12 levels are close to the normal conditions. This means a significant effect of high intensity interval training and Nano selenium supplementation on the oxidative stress in the testicles of rats.

IL-12 gene expression levels in the Nano selenium supplement and interval training group were significantly higher than the interval training alone group, supplement alone group, and dexamethasone group. Also, in the interval training group alone, the expression values of this gene were significantly higher than the Nano selenium supplement group and the dexamethasone

group, but no significant difference was seen between the supplement group alone and the dexamethasone group, which indicates a very important issue. It seems that the use of Nano selenium supplement alone does not have the ability to improve the pathological conditions caused by the use of dexamethasone, but intense interval training alone can significantly improve oxidative stress or develop the antioxidant defense of testicular cells. More studies are needed to confirm this hypothesis because oxidative stress and antioxidant defense were not measured in this study.

In general, the obtained results showed that dexamethasone injection, despite the anti-inflammatory effects and therapeutic cases, develops systemic inflammation in testicular cells, which increases the anti-inflammatory response of IL-10. In response to these conditions, interleukin 10 responds to existing conditions by suppressing interleukin 12. The more intense the environment is in terms of oxidative stress, the more is the amount of interleukin 10 and subsequently, the less is interleukin 12. However, periodic training interventions such as intense periodic training with the development of the internal and intrinsic antioxidant system of the body, which is very strong, has the ability to develop antioxidant defense and reduce cellular oxidative stress. These effects will be greater with antioxidant substances such as selenium. Also, inflammation is controlled by improving pathological conditions, but it seems that selenium supplementation alone does not have the ability to significantly improve inflammatory conditions in testicular cells, and for a more detailed investigation of this mechanism, more studies are needed by measuring antioxidant defense and Oxidative stress of testicular cells exposed to dexamethasone.

What is already known on this subject?

The use of dexamethasone increases the oxidative stress of the testicles and creates a pathological condition and an antioxidant imbalance in the testicular cells. The body's immune cells give a faster and stronger inflammatory response to these conditions causing an increase in IL-10 gene expression in testicular cells. With the presence of IL-10, the expression of interleukin 12 gene decreases because IL-10 is an anti-inflammatory factor.

What this study adds?

High intensity interval training and Nano selenium supplementation lead to improved immune function and possibly the ability to develop antioxidant defenses and reduce cellular oxidative stress.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol conformed to the Declaration of Helsinki and was approved by the animal care and use committee of Islamic Azad University, East Tehran branch (Ethical code IR.IAU.ET.REC.1401.011. 40).

Informed consent Animal study.

Author contributions

Conceptualization: A.H.P, SH.R.M.; Methodology: A.H.P, R.B, SH.R.M.; Software: A.H.P, R.B, SH.R.M.; Validation: A.H.P, R.B, SH.R.M.; Formal analysis: A.H.P, R.B, SH.R.M.; Investigation: A.H.P, R.B, SH.R.M.; Resources: A.H.P, R.B, SH.R.M.; Data curation: A.H.P, R.B, SH.R.M.; Writing - original draft: A.H.P, R.B, SH.R.M.; Writing - review & editing: R.B, SH.R.M.; Visualization: A.H.P, R.B, SH.R.M; Supervision: R.B, SH.R.M.; Project administration: A.H.P, R.B, SH.R.M.; Funding acquisition: A.H.P, R.B, SH.R.M.

References

Arabzadeh, E., Shirvani, H., Ebadi Zahmatkesh, M., Riyahi Malayeri, S., Meftahi, G. H., & Rostamkhani, F. (2022). Irisin/FNDC5 influences myogenic markers on skeletal muscle following high and moderate-intensity exercise training in STZ-diabetic rats. 3 Biotech, 12(9), 193. doi: https://doi.org/10.1007/s13205-022-03253-9

Coutinho, A. E., & Chapman, K. E. (2011). The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol, 335(1), 2-13. doi: https://doi.org/10.1016/j.mce.2010.04.005

Davoodi, M., Zilaei Bouri, S., & Dehghan Ghahfarokhi, S. (2021). Antioxidant effects of aerobic training and crocin consumption on doxorubicin-induced testicular toxicity in rats. J Family Reprod Health, 15(1), 28-37. doi: https://doi.org/10.18502/jfrh.v15i1.6075

Dehghani, F., Hossieni, S. A., Noorafshan, A., Panjehshahin, M. R., & Esmaeilpour, T. (2021). Effect of selenium on quantitative structural changes in dexamethasone-induced immunodeficiency rat models. Iran J Med Sci, 46(2), 128-135. doi: https://doi.org/10.30476/ijms.2020.81137.0

Dutta, S., Sengupta, P., Slama, P., & Roychoudhury, S. (2021). Oxidative stress, testicular inflammatory pathways, and male reproduction. Int J Mol Sci, 22(18). doi: https://doi.org/10.3390/ijms221810043

Farazandeh Nia, D., Hosseini, M., Riyahi Malayeri, S., & Daneshjoo, A. (2018). Effect of eight weeks of swimming training with garlic intake on serum levels of IL-10 and TNF-α in obese male rats. Jundishapur Scientific Medical Journal, 16(6), 665-671. doi: https://doi.org/10.22118/jsmj.2018.57830

Hajizadeh Maleki, B., & Tartibian, B. (2020). High-intensity interval training modulates male factor infertility through anti-inflammatory and antioxidative mechanisms in infertile men: A randomized controlled trial. Cytokine, 125, 154861. doi: https://doi.org/10.1016/j.cyto.2019.154861

Hamza, T., Barnett, J. B., & Li, B. (2010). Interleukin 12 a key immunoregulatory cytokine in infection applications. Int J Mol Sci, 11(3), 789-806. doi: https://doi.org/10.3390/ijms11030789

Hedayati, S., Riyahi Malayeri, S., & Hoseini, M. (2018). The effect of eight weeks of high and moderate intensity interval training along with aloe vera consumption on serum levels of chemerin, glucose and insulin in streptozotocin-induced diabetic rats: an experimental study. Journal of Rafsanjan University of Medical Sciences, 17(9), 801-814.

Iyer, S. S., & Cheng, G. (2012). Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Crit Rev Immunol, 32(1), 23-63. doi: https://doi.org/10.1615/critrevimmunol.v32.i1.30

Jankovic, D., Kugler, D. G., & Sher, A. (2010). IL-10 production by CD4+ effector T cells: a mechanism for self-regulation. Mucosal Immunol, 3(3), 239-246. doi: https://doi.org/10.1038/mi.2010.8

Kalhor, F., Arshadi, S., & Zafari, A. (2020). The effect of resistance training on Atrogin, eotaxin and IL-10 indices in obese women. Razi Journal of Medical Sciences, 27(3), 130-137.

Liu, J., Cao, S., Kim, S., Chung, E. Y., Homma, Y., Guan, X., . . . Ma, X. (2005). Interleukin-12: an update on its immunological activities, signaling and regulation of gene expression. Curr Immunol Rev, 1(2), 119-137. doi: https://doi.org/10.2174/1573395054065115

Malayeri, S. R., Nikbakht, H., & AliGaeini, A. (2014). Serum chemerin levels and insulin resistance response to highintensity interval training in overweight men. Bulletin of Environment, Pharmacology and Life Sciences, 3(Special Issue II), 385-389.

Mirsepasi, M., Baneifar, A. A., Azarbayjani, M. A., & Arshadi, S. (2019). The effects of high intensity interval training on gene expression of AKT1 and mTORc1 in the left ventricle of type 2 diabetic rats: an experimental study. Journal of Rafsanjan University of Medical Sciences, 17(12), 1119-1130.

Moayeri, P., Kojouri, G., Jafari dehkordi, A., & Ahadi, A. M. (2018). Study of Selenium nanoparticles and sodium selenite supplementation effects on expression of leptin gene in pregnant ewes placenta. Journal of Veterinary Research, 73(4), 475-482. doi: https://doi.org/10.22059/jvr.2019.228023.2592

Mohammadi, S., Rostamkhani, F., Riyahi Malayeri, S., & Shirvani, H. (2022). High-intensity interval training with probiotic supplementation decreases gene expression of NF-κβ and CXCL2 in small intestine of rats with steatosis. Sport Sciences for Health, 18(2), 491-497. doi: https://doi.org/10.1007/s11332-021-00829-5

Mohammadpour, A. A., & Mohammadeini, A. (2021). Protective effect of selenium in prednisolone testicular toxicity. Comparative Clinical Pathology, 30(5), 847-856. doi: https://doi.org/10.1007/s00580-021-03276-3

Nakagawa, T., Zhang, T., Kushi, R., Nakano, S., Endo, T., Nakagawa, M., . . . Nakayama, K. (2017). Regulation of mitosis-meiosis transition by the ubiquitin ligase β-TrCP in male germ cells. Development, 144(22), 4137-4147. doi: https://doi.org/10.1242/dev.158485

Nassan, M. A., Soliman, M. M., Aldhahrani, A., El-Saway, H. B., & Swelum, A. A. (2021). Ameliorative impacts of Allium cepa Linnaeus aqueous extract against testicular damage induced by dexamethasone. Andrologia, 53(4), e13955. doi: https://doi.org/10.1111/and.13955

Noreen, S., Maqbool, I., & Madni, A. (2021). Dexamethasone: Therapeutic potential, risks, and future projection during COVID-19 pandemic. Eur J Pharmacol, 894, 173854. doi: https://doi.org/10.1016/j.ejphar.2021.173854

Orazizadeh, M., Khorsandi, L. S., & Hashemitabar, M. (2010). Toxic effects of dexamethasone on mouse testicular germ cells. Andrologia, 42(4), 247-253. doi: https://doi.org/10.1111/j.1439-0272.2009.00985.x

Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., . . . Bitto, A. (2017). Oxidative Stress: harms and benefits for human health. Oxid Med Cell Longev, 2017, 8416763. doi: https://doi.org/10.1155/2017/8416763

Prihatno, S. A., Adi, Y. K., & Budipitojo, T. (2020). Immunolocalization of IL-6 and IL-10 in the testicular tissue of testicular dysfunction rat treated with secretome. J Adv Vet Anim Res, 7(3), 514-520. doi: https://doi.org/10.5455/javar.2020.g448

Qazi, I. H., Angel, C., Yang, H., Zoidis, E., Pan, B., Wu, Z., . . . Zhou, G. (2019). Role of selenium and selenoproteins in male reproductive function: a review of past and present evidences. Antioxidants (Basel), 8(8). doi: https://doi.org/10.3390/antiox8080268

Ramamoorthy, S., & Cidlowski, J. A. (2016). Corticosteroids: mechanisms of action in health and disease. Rheum Dis Clin North Am, 42(1), 15-31, vii. doi: https://doi.org/10.1016/j.rdc.2015.08.002

Ramírez-Acosta, S., Selma-Royo, M., Collado, M. C., Navarro-Roldán, F., Abril, N., & García-Barrera, T. (2022). Selenium supplementation influences mice testicular selenoproteins driven by gut microbiota. Sci Rep, 12(1), 4218. doi: https://doi.org/10.1038/s41598-022-08121-3

Riyahi Malayeri, S., Abdolhay, S., Behdari, R., & Hoseini, M. (2019). The combined effect of resveratrol supplement and endurance training on IL-10 and TNF- α in type 2 diabetic rats. Razi Journal of Medical Sciences, 25(12), 140-149.

Riyahi Malayeri, S., Azadniya, A., & Rasaee, M. J. (2019). Effect of eight-week high intensity interval training and resveratrol intake on serum adiponectin and resistin in type 2 diabetic rats. Iranian Journal

of Diabetes and Lipid Disorders, 18(1), 8-1.

Riyahi Malayeri, S., & Saei, M. (2019). Changes in Insulin resistance and serum levels of resistin after 10 weeks high intensity interval training in overweight and obese men. Sport Physiology & Management Investigations, 10(4), 31-42.

Soleimani Ghaleh, O., Riyahi Malayeri, S., & Abedi, B. (2022). The effect of interval training and Nano selenium supplementation on the expression of testicular HSP70 and PGC-1α genes in dexamethasone induced rats. Medical Journal of Mashhad University of Medical Sciences, 65(2), -. doi: https://doi.org/10.22038/mjms.2022.21339

Steen, E. H., Wang, X., Balaji, S., Butte, M. J., Bollyky, P. L., & Keswani, S. G. (2020). The Role of the anti-inflammatory cytokine interleukin-10 in tissue fibrosis. Adv Wound Care (New Rochelle), 9(4), 184-198. doi: https://doi.org/10.1089/wound.2019.1032

Taherkhani, S., Suzuki, K., & Castell, L. (2020). A short overview of changes in inflammatory cytokines and oxidative stress in response to physical activity and antioxidant supplementation. Antioxidants (Basel), 9(9). doi: https://doi.org/10.3390/antiox9090886

Tugues, S., Burkhard, S. H., Ohs, I., Vrohlings, M., Nussbaum, K., Vom Berg, J., . . . Becher, B. (2015). New insights into IL-12-mediated tumor suppression. Cell Death Differ, 22(2), 237-246. doi: https://doi.org/10.1038/cdd.2014.134