



The Various Mechanisms by Which Exercise-Induced Fatigue (EIF) Affects Spermatogenesis Through Testosterone

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Abstract

Currently, a great number of researches have proven that the EIF triggered by inappropriate and excessive exercise will affect normal function of the male reproductive system, resulting in various disorders or increasing disease risks. Reproductive system and motor system are highly correlated. Now, it is mainly considered that the testicular cell is modulated via hypothalamus-hypophysis-gonad(HPG) axis in the process of exercise, which involves the whole male reproductive system and affects spermatogenesis. However, there are many mechanisms leading to EIF, including hormonal levels, lactic acid accumulation, oxidative stress, calcium ion disorder, and inflammatory responses. These mechanisms interact with each other and can directly or indirectly affect spermatogenesis through testosterone hormones in various ways, with the majority having a negative impact. This ultimately leads to dysfunction of spermatogenesis and decreased sperm quality in the male reproductive system under the state of EIF. Therefore, this article reviews various theoretical mechanisms leading to EIF and their intervention methods on spermatogenesis through testosterone hormones, explaining the correlation between EIF and spermatogenesis from the perspective of endocrine regulation, providing new directions for the prevention and treatment of related symptoms.

Keywords EIF · Testosterone · Male reproductive system · Exercise · Spermatogenesis

Introduction

With the global economic development, improvement of living standards, sustained development and propaganda of sports competition, and growing popularity of science and health concept, more and more people have maintained and promoted their own health through fitness and sports. However, the cases regarding the EIF triggered by unscientific, abnormal and excessive exercise happen all the time, and most of the people in the cases are male. Moreover, in addition to affecting other organs of body, EIF may affect

testicular function via various mechanisms, further having an adverse effect on the male reproductive system, and may lead to dyszoospermia, reduction of sperm mobility or relevant secondary testicular disease, thus affecting life and even offspring.

EIF refers to the decline of physical working capacity induced by exercise and usually belongs to a kind of normal physiological mechanism [4]. Many hypotheses have been proposed for the relevant mechanisms triggering EIF, including mutation theory, exhaustion theory, plugging theory, free radical theory, calcium disturbance theory, and protective inhibition theory. Currently, it is generally believed that exercise has the most impact on the male reproductive system in hypothalamus-hypophysis-gonad axis (HPG axis). Exercise affects HPG axis and testicular cells via interaction of hormones such as testosterone and muscular tissue, thus directly affecting the male reproductive system [101] and leading to the dyspermatogenesis. Such a mechanism plays an important role in EIF. In addition to the direct effects of the HPG axis, testosterone is also affected by other mechanisms of EIF and impacts the normal progression of spermatogenesis. Studying these has important

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clinical significance. Therefore, to prevent and treat male reproductive dysfunction resulting from EIF and promote the relevant research, various mechanisms based on which EIF affects spermatogenesis are reviewed in this thesis. Refer to Figs. 1 and 2 for retrieval method and mechanism overview, respectively.

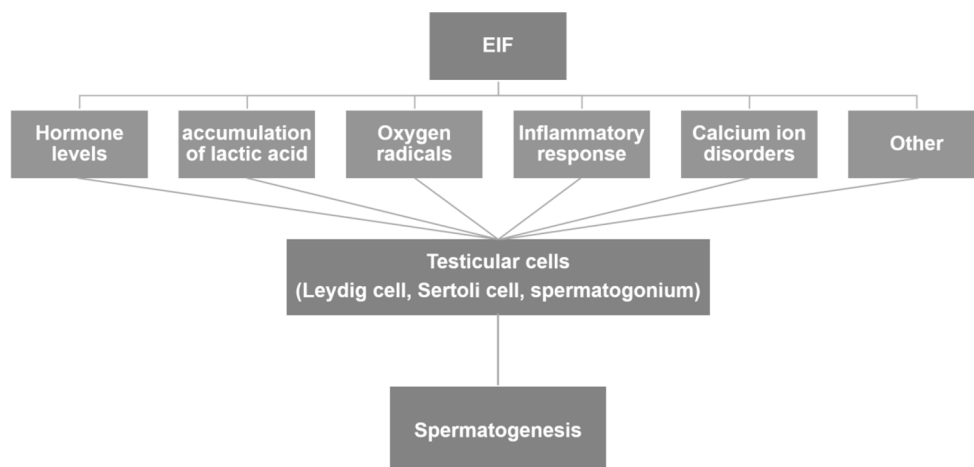
Impact of EIF on Spermatogenesis

EIF Affects Spermatogenesis via Hormone Level Change

In the process of exercise, the level of various stress and emergency hormones would change [74], including testosterone, cortisol, luteinizing hormone, and follicle stimulating hormone. Those hormones affect reproductive function via HPG axis to a large extent [39]. Under normal circumstances, GnRH neuron of HPG axis generates GnRH to play a core role in HPG axis. GnRH binds with the membrane

Fig. 1 Review method

Review Method
Retrieval time: Author retrieved literature at the beginning of January 2024.
Retrieval database: PubMed, Google scholar, Web of Science, CNKI, and CBM.
Time limit for literature retrieval: January 1990- January 2024.
Search terms: "EIF, male reproductive system, exercise, testosterone, testicular cell, fatigue mechanism, and other words" as keywords.
Types of literature retrieval : Animal experiment, clinical research, theoretical review, visualization research and questionnaire.
Inclusion criteria: ① Literature in which the relevant mechanism of exercise with EIF, male reproductive system and testicular interstitial cells is studied; ② articles which determine the impact of exercise and EIF on the male reproductive system and testicular interstitial cells via animal experiment; ③ review literature which summarizes the relevant mechanism of EIF and testicular interstitial cells; ④ literature in which the clinical treatment of the male reproductive system dysfunction resulting from EIF is studied; ⑤ literature regarding the questionnaire/epidemiological investigation related to EIF and male reproductive system; and ⑥ literature or references in which mechanism correlation between EIF and testicular interstitial cells is not directly described but contributions have been made to its research.
Exclusion criteria: ① Repeated literature with over-correlation; ② literature with non-rigorous data; ③ literature which is illogical or inconsistent with facts; ④ literature which has been falsified or has theoretical negligence; ⑤ literature without practical significance or with low quality; and ⑥ articles which don't conform to inclusion criteria.
Data integration and extraction : Repeated literatures shall be eliminated, and high-quality literatures among similar literatures are screened for integration analysis. Articles shall be intact, thinking logic shall be clear and distinct, and the articles shall be objective and innovative and shall not be out-of-date. They shall be directly or indirectly correlated with the review topic, have certain quality, and can show the latest research progress.

Fig. 2 Mechanism overview

receptor on hypophysis gonadotropin and stimulates the biosynthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Testosterone in the blood of men is mainly secreted by testicular interstitial cells, adrenal cortex, etc. Testosterone could directly act on associated receptor of muscle cells and then affect musculature cells. Spermatogenesis of Sertoli cells and normal development of spermatogonium in testosterone cells also requires the endorsement of testosterone [14]. Moreover, FSH and LH in HPG axis are basic hormone regulators of testicular function. Testosterone would complete negative feedback regulation on the HPG axis to affect LH and FSH. Testosterone with overconcentration and hypoconcentration would inhibit and promote the generation of LH and FSH, respectively. LH and FSH work via their receptors in Sertoli cells and interstitial cells, and can promote the formation of testosterone and coordinate with testosterone to promote spermatogenesis.

Testosterone is primarily regulated and controlled by HPG axis in a quiet state, but hypothalamus-hypophysis-adrenal axis (HPA axis) increases the regulatory effect on testosterone in the exercise process [86] so that the testosterone level is associated with the exercise intensity level [93]. Under different exercise intensities, the testosterone level is higher in the process of exercise than that in a relatively resting state. This study [15] indicates that endurance athletes with higher training intensity have lower testosterone levels at rest, and ultra-endurance exercise can cause a sharp decline in testosterone levels, significantly inhibiting the function of the hypothalamic-pituitary axis. The testosterone level becomes lower to different degrees within a period after exercise. Since EIF usually results from long-term high-strength and high-frequency exercise, the testosterone level in the EIF state is far lower than that at the normal level [7, 96]. Under EIF conditions, the negative feedback regulation of the HPG axis is one of the main reasons for the inhibition of hypothalamic-pituitary axis function. That

is, HPG axis inhibits the kisspeptin of hypothalamus and mRNA level of neurokinin B. Both of them are regulatory factors of gonadotropin-releasing hormone (GnRH), but they don't affect the mRNA level of kisspeptin receptor or neurokinin-3 in hypothalamus [35]. The HPA axis also has a similar negative feedback regulation mechanism. In addition to the inhibition of synthetic functions in the HPG and HPA axis of hypothalamus, abnormal expression of LH/CG receptor P450 in testicular interstitial cells [27], reduction in testosterone reserves of interstitial cells, abnormalities in key enzymes involved in the testosterone biosynthesis pathway [42], and other related mechanisms associated with EIF such as oxidative stress, inflammatory factors, and calcium ion imbalances can impair the normal secretion of testosterone by testicular interstitial cells.

Prolonged low testosterone levels can have adverse effects on testicular cells, and may even lead to apoptosis and aging of testicular cells. Since intratesticular testosterone plays a major role in spermatogenesis, its low levels can significantly cause abnormalities in spermatogenesis [13]. It is difficult for the Sertoli cells to develop in normospermia and spermatogonium to develop in the process of normal fission and mature development, and spermatogenesis is impeded. Untimely treatment and improvement may further lead to the decline of sperm motility, low gonadal activity, prostatic disease [61], developmental retardation and agenesis of the reproductive system, etc.

To sum up, EIF would affect the HPG axis, HPA axis and testicular interstitial cells via many approaches, thus leading to a low level of testosterone, while testosterone plays an important role in the male reproductive system. The low level of testosterone would lead to the abnormal spermatogenesis and reproductive dysfunction, as shown in Fig. 3.

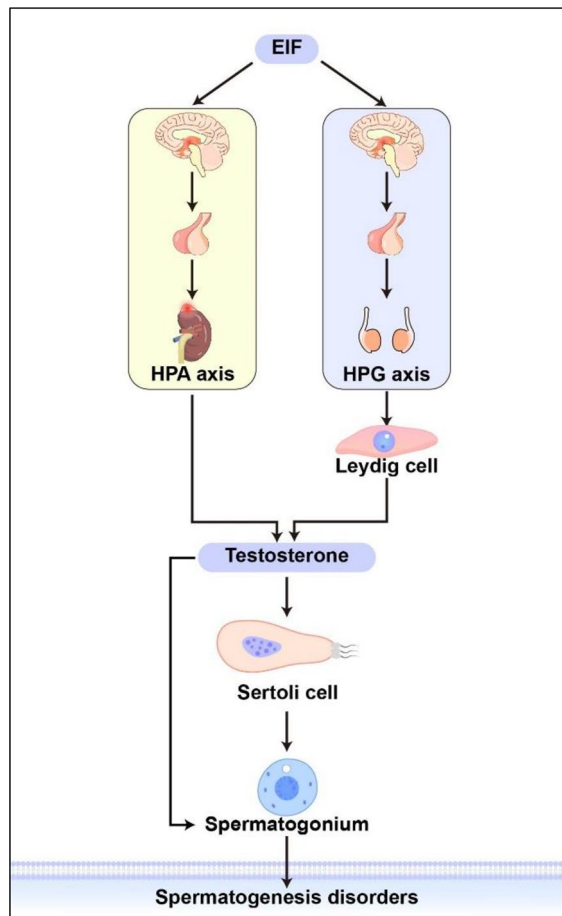


Fig. 3 EIF affects spermatogenesis via hormone level change

EIF Affects Spermatogenesis via Lactic Acid Accumulation

Among mechanisms regarding EIF, blocking theory (metabolite accumulation theory) always has an important position. The intensification of related energy metabolism activities (glycolysis) of body leads to the overaccumulation of some metabolites (including lactic acid) which can't be eliminated in a timely manner. As a result, the working capability of muscle and other tissues becomes lower [94], generating EIF. During high-intensity exercise, glycolysis activity of body cells is enhanced, generating more lactic acid and leading to lactic acid accumulation. After exercise, the H^+ generated by lactic acid dissociation increases, which leads to the decline of pH value in muscle, inhibition of glycolysis and insufficient supply of ATP. Excessive H^+ could competitively inhibit the combination of Ca^{2+} and troponin, resulting in excitation-contraction decoupling and EIF. Moreover, some research results indicate that skeletal muscles could have fatigue without acidosis [20] and advance acidizing treatment wouldn't speed up fatigue of skeletal muscles [11]. Even some research results indicate

that lactic acid isn't a kind of metabolic waste. It is a kind of effective approach of distributing substrate and coordinating inter-tissue oxidation reduction state in the steady state of energy metabolism [25].

Despite of the effect of lactic acid on the motor system, increased lactic acid could enter the blood circulation system via lactic acid shuttle and reach the whole body to affect other systems [10]. The results of this animal experiment [59] indicate that high-intensity exercise leads to a significant increase in lactic acid levels in testicular tissue, proving that the lactic acid levels in the reproductive system are also affected by the exercise system. In testicular cells, lactic acid often serves as an energy source and also improves spermatogenesis, enhances RNA and protein synthesis in germ cells, and inhibits apoptosis of germ cells [91]. Some research results indicate that lactic acid could affect the testosterone generation process of testicular interstitial cells [55]. In the research, the plasma testosterone level of male rats during exercise becomes higher partially due to the direct role of lactic acid by increasing production of cAMP in testosterone and the independent stimulating role of LH. In other words, lactic acid can promote the testosterone to generate testicular interstitial cells. However, it is still questionable whether the same effects apply to humans. The blood-testis barrier (BTB) has a similar structure in mammals, but there are differences in the actual substances transported and the locations of transport proteins. In the EIF state, the impact of high-concentration lactic acid on testicular interstitial cells is unknown in research. In some relevant researches, the promoting effect of accumulated high-concentration lactic acid on testosterone generation of testicular interstitial cells would decline to some extent [49] and the rise of corticosterone resulting from EIF would [93] decrease the promoting effect of lactic acid for testicular interstitial cells [12]. It is important to note that under EIF, lactic acid can still promote testosterone production, albeit with a diminished effect.

The change of testosterone level with lactic acid accumulation would affect Sertoli cells and spermatogonium, thus affecting spermatogenesis. In combination with previous research that lactic acid may not belong to metabolic waste [25], it may be argued that lactic acid could protect body to a certain extent and could relieve testosterone hypoconcentration in the EIF state. However, it cannot be definitively concluded that the accumulation of lactic acid under EIF is absolutely beneficial for spermatogenesis, as there is currently a lack of research verifying the levels of lactic acid in testicular tissue when the human body is in EIF. If the concentration of lactic acid is too high, it may also lead to Acidosis, chronic inflammation, and other secondary symptoms [54, 99].

In summary, lactic acid accumulation in the body can affect spermatogenesis by affecting the testosterone secretion process of interstitial cells. From the perspective of testosterone regulation alone, this mechanism is beneficial as it promotes testosterone secretion and sustains spermatogenesis, as shown in Fig. 4.

EIF Affects Spermatogenesis via Oxidative Stress and Ferroptosis

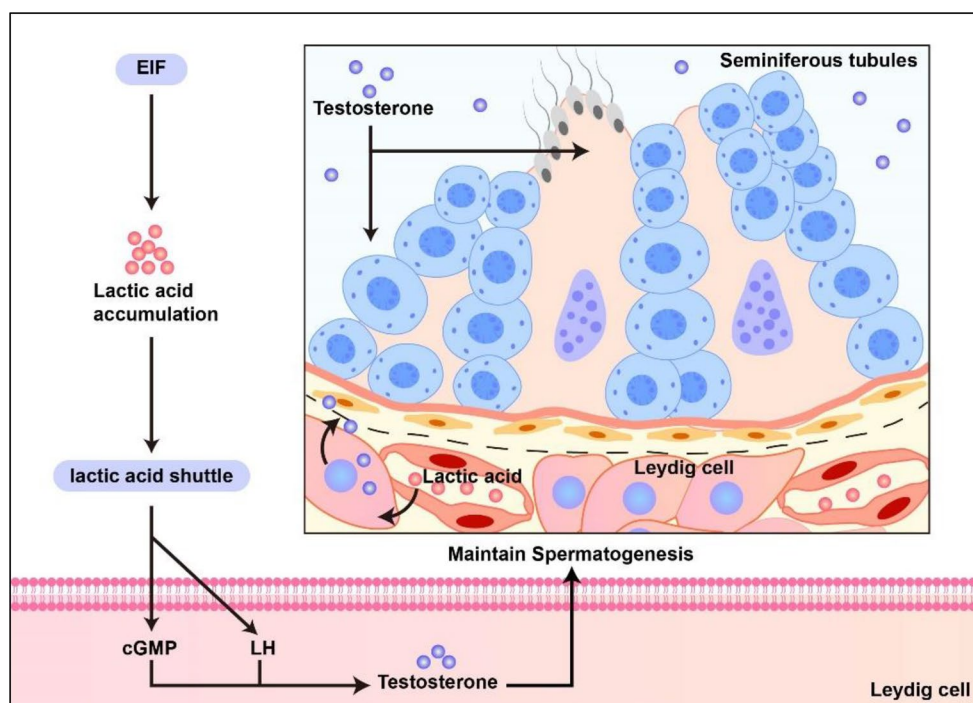
Oxidative Stress and Ferroptosis of EIF

As a kind of substance lacking electrons (unsaturated electronic matter), free radical (ROS) [44] competes for electrons after entering body. If the electrons of cellular protein molecule are eliminated, protein would connect to branched chain for alkylation, leading to cytopathy. Under normal conditions, free radicals are in a dynamic equilibrium state in body. If such equilibrium is broken, overgeneration of free radicals would lead to oxidative stress and trigger organism lesion [63]. Oxidative stress refers to the disequilibrium between oxidizing agent and antioxidant, in which oxidizing agent predominates, leading to the destruction of conduction and control of oxidation reduction signal and/or molecular damage [38]. Many research results have proven that muscle movement would promote the generation of free radicals. Various cells in body would generate oxygen radicals more or less in the process of exercise, but skeletal muscle is prime source of ROS possibly due to lower elimination ability of free radicals by mitochondria with

the enhancement of glycolytic activity [69]. It is commonly believed that mitochondria dominates in ROS generation process of skeletal muscle. Skeletal muscle cells lead to the reduction of ATP generation and higher glycolytic activity due to hypoxia upon high-intensity exercise of body, and then cause overgeneration of xanthine oxidase, while xanthine oxidase would generate a great deal of oxygen radical and hypoxanthine due to ATP decomposition [28]. Different degrees of free radical clearance obstacles occur based on different exercise intensity and hypoxia duration. After high-intensity exercise, lipid peroxidation between free radicals increasing in vivo and polyunsaturated fatty acids in biological film increases lipid peroxides such as malondialdehyde [95], then the increased malondialdehyde would damage cells and finally lead to fatigue due to above factors. Therefore, oxygen radical and oxidative stress are deemed one of important mechanisms for EIF [67]. In fact, during appropriate exercise, free radicals may not solely have negative effects [70]. However, in the context of the mechanisms related to EIF, this review primarily focuses on their adverse impacts.

Recent research results show the increase of oxygen radicals would lead to ferroptosis, in which a kind of small molecule-induced oxidative cell death is the iron-dependent process resulting from generation and degradation imbalance of reactive oxygen of intracellular lipid [22], and is deemed one of apoptosis patterns resulting from the above oxygen radical. The skeletal muscles in the fatigue state generate a great deal of free radicals due to the above oxidative stress, and cystine uptake disorder and other problems

Fig. 4 EIF affects spermatogenesis via lactic acid accumulation



cause the decline of glutathione (GSH) activity [9] and the reduction of the scavenging ability of free radicals, thus decreasing the decline of activity of glutathione peroxidase 4 (GPX4). While GPX4 could transform toxic lipid hydroperoxide (L-OOH) into nontoxic lipidol (L-OH) to prevent Fe²⁺-dependent lipid ROS from accumulating on membrane lipid, thus greatly inhibiting ferroptosis [83]. Therefore, decline of GPX4 activity further increases and accumulates ROS and lipid peroxide in cells till cells die, while the imbalance between GSH and GPX4 is deemed one of key factors for ferroptosis, and coenzyme Q10 system [8] and tetrahydrobiofuran (BH4) system [41] also participate in the process. Those factors jointly promote and aggravate the EIF symptom [87].

Additionally, abnormal iron metabolism is deemed one of important causes for ferroptosis [78], and the increase of free Fe²⁺ would induce more cell ferroptosis. But some research results indicate that exercise can improve human iron metabolism. This research [77] indicates that the level of serum free Fe²⁺ significantly rises during intense physical activity; however, during the recovery period, the Fe²⁺ level is lower than the normal value. When free Fe²⁺ increases, hepcidin in the brain (Hepc) could be increased via exercise to improve iron metabolism [90]. Some research results indicate the rise of inflammatory factor level in body after high-strength and high-frequency exercise intervention leads to the increase of hepatogenic Hepc and the decline of serum iron and ferritin [50], which may be a kind of self-protection mechanism of body to reduce the skeletal muscle or other tissue cells of ferroptosis due to the increase of oxygen radicals in the fatigue state.

Oxidative Stress and Ferroptosis of the Male Reproductive System

Few studies have examined the impact of exercise on oxidative stress in testicular tissue. These two animal experimental studies [36, 97] indicate that exercise-induced oxidative stress impairs testicular reproductive function, resulting in elevated levels of oxidative stress in the testes, abnormal testosterone synthesis, and disrupted spermatogenesis following high-intensity exercise. This study involving human subjects indicates that the oxidative stress markers in athletes' semen samples remain abnormal 30 days after intensive training [58]. Clearly, the oxidative stress that occurs during high-intensity exercise is not limited to skeletal muscle cells, and the vascular endothelial cells around muscular tissue would also generate free radicals to directly or indirectly enter blood circulation for oxidative stress of other parts of body [18, 76].

In general, few free radicals exist in sperm and spermatogenic cells, which is normal and could modulate the

function of the reproductive system to a certain extent [1], but excessive free radicals would have an adverse impact on sperm and spermatogenic cells, including the increase of free radicals resulting from EIF. This article suggests that high-intensity training may have adverse effects on sperm morphology without affecting the integrity of sperm DNA, which might be related to lipid peroxidation [31]. As mentioned above, free radicals could perform lipid peroxidation with polyunsaturated fatty acids in biological film, finally damaging biofilm, while the surface of sperm membrane is also rich in polyunsaturated fatty acids, so sperm membrane would be attacked by free radicals. For spermatogonium, biological film is attacked. Moreover, excessive free radicals would lead to cell apoptosis [60]. Finally, decline of sperm motility, reduction of quantity of sperms, and others trigger the dysspermatogenesis.

For the testosterone, excessive free radicals could reduce the activity of testosterone synthetase in testicular interstitial cells and even make the cells die to reduce the testosterone synthesis [103], because related steroid in testicular interstitial cells is extremely sensitive to oxidative stress [53]. Although some studies have shown that appropriate endurance exercise can reduce testicular ROS and maintain testosterone levels [5], this is clearly in contrast to the situation after high-intensity exercise [97]. Moreover, some research results indicate that testicular interstitial cells have a similar effect via exogenous injection of peroxide [3]. The above research results may indicate that increase of extracellular free radicals in the internal environment resulting from EIF could also affect testicular interstitial cells and reduce the testosterone synthesis, and the mechanism may be one of causes for low testosterone level in the fatigue state.

Many studies have shown that ferroptosis is not uncommon in testicular cells [100, 102]. Iron metabolism abnormality, lipid peroxidation, oxidative stress, mitochondria injury, and others would lead to or aggravate the ferroptosis of testicular cells [17]. However, one experiment [75] indicated that although ROS-induced testicular lesions increase iron accumulation, molecular evidence does not show the involvement of ferroptosis. Regrettably, there is a lack of direct research indicating the Fe²⁺ levels and ferroptosis in testicular tissue under EIF. Therefore, despite the high correlation between ferroptosis and oxidative stress, it cannot be concluded that EIF definitely causes ferroptosis in testicular cells. Another aspect related to EIF that is worth studying is whether the hypothalamic-pituitary axis exhibits abnormal iron metabolism. Iron accumulation in the hypothalamic-pituitary axis may affect the HPG and HPA axes, leading to decreased levels of FSH, LH, and testosterone [68, 84, 98].

Excessive free radicals can lead to secondary phenomena such as inflammatory reactions [52], and ultimately result in abnormal spermatogenesis, oligospermia, and

asthenospermia in the male reproductive system due to various factors, mainly including damage to Leydig cells that impairs their ability to provide Sertoli cells and spermatogonia with adequate levels of testosterone. In short, dys-spermatogenesis in the EIF state possibly results from ROS excessive generation. But the oxidative stress in testicular tissue during EIF and whether ferroptosis occurs still need to be verified and studied, as shown in Fig. 5.

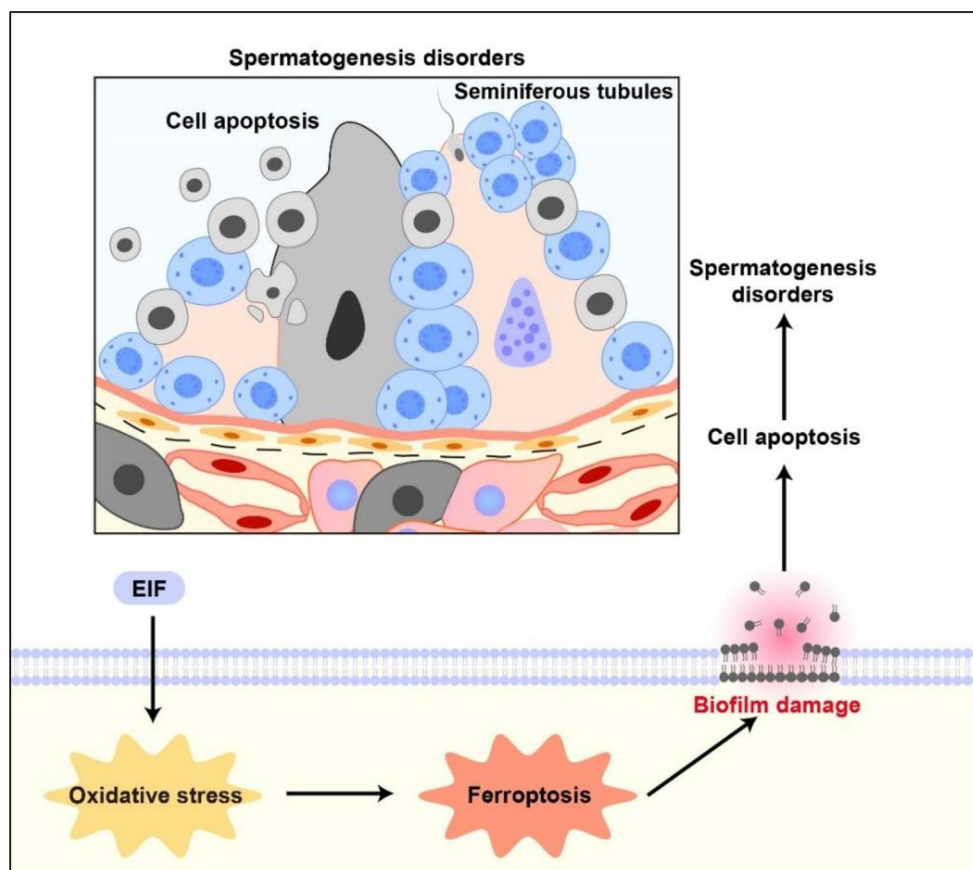
EIF Affects Spermatogenesis via Inflammatory Reaction

Exercise would increase systematic and partial inflammatory cells and inflammatory factor, particularly the acute high-intensity exercise [81]. In the activation mechanism of inflammatory reaction, free radicals generated in skeletal muscle activity are usually deemed important factor and can prolong muscular inflammation resulting from acute exercise [6]. Muscle resident cells and vascular endothelium release and generate inflammatory mediator of chemotactic signaling to drive transportation of white blood cells to muscular tissue [40]. After acute high-intensity exercise, inflammatory reaction is characterized by a higher blood IL-6 level, better neutrophil migration ability, and aggregation of white blood cells to skeletal muscle blood vessels

[19]. Some research results prove that such inflammation resulting from exercise actually can restore homeostasis and improve physical ability [21]. Moreover, inflammatory reaction could have a significant effect on EIF. Lots of research results indicate that inflammatory reaction wouldn't disappear quickly after high-intensity exercise, and the levels of various inflammatory cells and factors in the fatigue state are significantly higher than those in the normal state [19, 30, 47]. The higher the exercise intensity is, the higher the fatigue degree is, and the more the inflammatory factors are [48], in which IL-6 is the most representative [24]. Some research results indicate that the increase of IL-6 in exercise leads to higher degree and occurrence rate of fatigue [71]. Besides, as one of patterns of manifestation of EIF, DOMS is also considered to be triggered by a series of inflammatory reactions in the process of exercise [23], and lower inflammatory reaction degree can significantly reduce the fatigue or injury [51]. Therefore, inflammatory reaction may have a bigger negative impact on EIF.

Inflammatory factors increased in blood circulation in the EIF state would affect the male reproductive system which is closely associated with inflammatory reaction. This animal experiment [64] very directly points out that high-intensity exercise can lead to inflammation in testicular tissue, and it has a correlation with interstitial cells and testosterone.

Fig. 5 EIF affects spermatogenesis via oxidative stress and ferroptosis



This study [29] involving human subjects also indicates that long-term training athletes still exhibit elevated levels of IL-1 β , IL-6, and IL-8 in their semen samples 30 days after the conclusion of training.

There are also many studies on treating inflammation through exercise [33]. However, in the EIF state, inflammatory reaction has a bigger negative impact on the reproductive system. Under normal circumstances, IL-1, IL-6, TNF, and other substances could retain spermatogenesis, facilitate the generation of glandular hormone and testosterone, modulate blood-testis barrier, perform immunomodulation, etc [85]. But, under pathological condition, those factors would play a negative role. Many inflammatory factors would not only directly injure testicular tissue and lead to the abnormality of spermatogenesis function, but also affect the HPG axis in various methods and have an adverse impact on hormone level [43], further negatively affecting spermatogenesis. For example, some research results indicate that the increase of IL-6 would inhibit the differentiation of mesenchymal stem cells in testis of rats, hinder the regeneration of interstitial cells, and lower the serum testosterone level to a certain extent [66], which will result in spermatogenesis dysfunction eventually. This may be associated with the significant increase in IL-6 levels under EIF conditions mentioned earlier [24]. In other aspects, inflammatory factors are highly correlated with free radicals, and its interaction with free radicals would further aggravate the testicular cell injury, even lead to orchitis and other diseases [65]. In the EIF state, the body's free radical contents would increase,

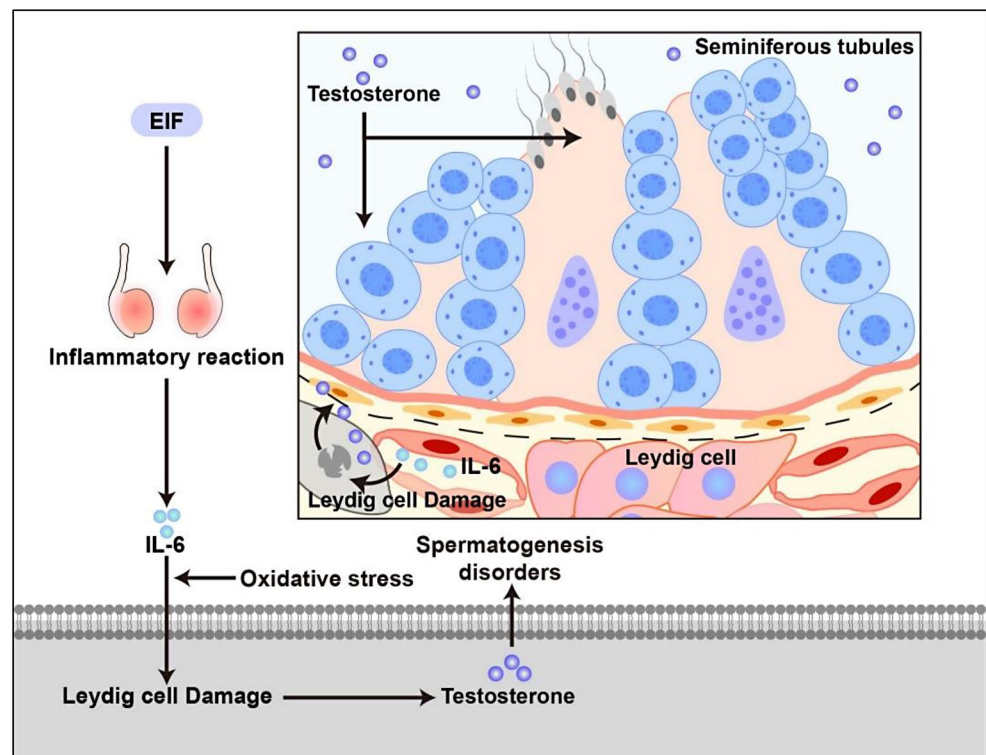
so EIF may also promote the process. Moreover, the athletes in the previously mentioned experiment [29] still exhibited lower levels of semen volume, sperm motility, sperm morphology, sperm concentration, and sperm count 30 days after recovery. This directly demonstrates that the inflammatory response under EIF conditions can have adverse effects on spermatogenesis.

In short, the inflammatory reaction is treated as one of the male reproductive system dysfunctions in the EIF state. The inflammatory factors attached to EIF would affect testicular tissue with various methods, and finally promote dys-spermatogenesis, orchitis, gonadal hormone abnormalities, oligospermia and asthenospermia, and other diseases, as shown in Fig. 6.

EIF Affects Spermatogenesis via Calcium Disturbance

Calcium disturbance theory refers to the steady-state anomaly of Ca^{2+} in skeletal muscle cells due to attack of free radical and lipid peroxidation in the EIF state. As a result, the concentration of Ca^{2+} in cells significantly increases, thus inhibiting the mitochondria activity. The generation of ATP is inhibited, which further aggravates the disorder of Ca^{2+} in cells, promoting fatigue [79]. Excessive Ca^{2+} in skeletal muscle cells would break the equilibrium between sarcoplasmic retic and myoneme, and lead to dysfunction of muscle movement, DOMS, etc. Some research results indicate that the concentration of Ca^{2+} of blood, liver, and others in

Fig. 6 EIF affects spermatogenesis via inflammatory reaction



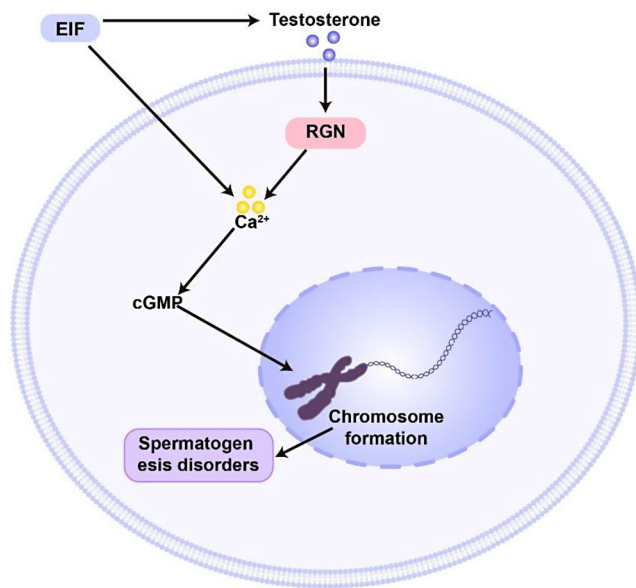


Fig. 7 EIF affects spermatogenesis via calcium disturbance

the parts rather than skeletal muscle in the EIF state would increase significantly [89]. The blood flow of the testicular may be affected.

Calcium ions are also important for the male reproductive system. In addition to affecting the biochemical activity of testicular cells, Ca^{2+} mainly plays an important role in spermatogenesis and acrosome reaction [37, 62]. In respect of the EIF affecting the approach of testicular cells via Ca^{2+} , some research results indicate that Regucalcin (RGN, a kind of calcium-binding protein) expressed by male germinal tissue may directly play a role in spermatogenesis as a medium of androgen action [46], it can modulate the concentration of Ca^{2+} in cells to guarantee the stability of Ca^{2+} , and is regulated and controlled by steroid sex hormone [92]. In testis, testosterone would promote the expression of RGN [45].

In consideration of the impact of EIF on the gonadal hormone axis, there may be complex contact among Ca^{2+} , testosterone and EIF. This animal experiment [56] demonstrates that EIF has a significant impact on the Ca^{2+} levels in testicular tissue and is associated with testosterone. However, the specific mechanisms between EIF and Ca^{2+} have not been clearly explained. The decrease of testosterone resulting from EIF may inhibit the expression of RGN in testicular tissue, further decreasing its regulation ability of steady state of Ca^{2+} . Moreover, the higher concentration of Ca^{2+} in surrounding environment of cells raises the Ca^{2+} level of testicular cells significantly. In the membrane guanylate cyclase of testicular cells, calcium modulates the membrane guanylate cyclase (ROS-GC) which is mainly affected by the level of Ca^{2+} in cells. When Ca^{2+} level becomes higher, ROS-GC activity will decline, further reducing the expression of cGMP. cGMP plays an important

role in spermatogenesis and affects the normal formation of chromosome in spermatogenesis process [37]. Additionally, the phosphorylation of p38 is associated with Ca^{2+} and cGMP. The p38 MAPK signaling pathway in testicular interstitial cells is considered crucial for regulating their function and survival [57]. The activity of p38 MAPK is affected by levels of Ca^{2+} [88]. An increase in p38 MAPK can further activate pathways such as p16, p21, and NF- κB , leading to apoptosis and aging of interstitial cells, which affects testosterone synthesis, secretion, and fertility functions. In other words, Ca^{2+} disorder of testicular cells could make spermatogenesis abnormal via such an approach.

In short, the calcium disturbance resulting from EIF may implicate the testicular tissue cells and trigger spermatogenesis dysfunction, etc. However, research on how EIF directly affects spermatogenesis through calcium disturbance is still lacking. Especially lacking are experiments related to human subjects, as shown in Fig. 7.

Other Mechanisms of EIF and its Possible Impact on Spermatogenesis

According to the protective inhibition theory, feeling of fatigue is generated in the inhibition of partial neuronal activities to protect cortical tissue when the motor neuron is highly active and motor areas of the cerebral cortex keep sustained excitation during exercise [82]. It may deeply affect the male reproductive system in neurological and psychological aspects including erectile dysfunction, and sexual dysfunction. Such indirect impact may not significantly affect spermatogenesis.

According to the exhaustion theory, a lot of energy materials are consumed in exercise, and failure to replenish the blood glucose, glycogen, and other substances in a timely manner at the end of exercise would affect the normal activity of brain and skeletal muscle and lead to generation or aggravation of fatigue. Currently, many research results indicate that there is complicated connection among blood glucose, insulin and androgen [2], and there are many other researches which prove that exercise can improve the reproductive function of men suffering from diabetes [73]. Based on those research results, it can be speculated that EIF can affect testicular cells and further affect spermatogenesis via association of blood glucose, insulin and sex hormone as a symptom resulting from overexercise, but it probably has a bigger negative impact.

In addition to the above mechanism theories, EIF comprises nerve-muscle junction point fatigue theory, peripheral multilevel influence, mutation theory, etc [16]. Which are of important significance in generating EIF. However, currently, those theories are seldomly associated with spermatogenesis for study, there is little research significance,

or they have repetition with other mechanism theories. Nevertheless, undiscovered relevant mechanisms contained by them cannot be excluded.

Conclusion and Outlook

It is evident that all mechanisms are inseparable from the role of testosterone, which links these mechanisms together. The impact of EIF on spermatogenesis results from many approaches, including hormone, lactic acid, inflammation, free radicals, iron metabolism, and calcium disturbance. Those approaches are mostly from exercise process and directly or indirectly act on testicular cells via testosterone in different methods when inducing EIF, finally leading to the corresponding change.

To address the damage to reproductive function caused by EIF, focus can be placed on both EIF itself and testosterone. Improving EIF can ameliorate the spermatogenic abnormalities it causes. Physical treatments such as hot baths, massages, and relaxation exercises can be effective. Pharmacologically, vitamin C intake might be a good option [72], as it can alleviate EIF through its antioxidant properties and maintain normal spermatogenic function [26]. Supplementation with Branched-Chain Amino Acid (BCAA) can alleviate fatigue while maintaining testosterone levels by mitigating oxidative stress [34]. Regulating testosterone can have a more direct impact on spermatogenesis and can also alleviate EIF to some extent. Improving spermatogenesis through testosterone primarily involves pharmacological approaches. In addition to the aforementioned vitamin C, drugs like icariin can also maintain spermatogenesis by upregulating testosterone levels [80], or exogenous testosterone [32] intake under the guidance of professional medical personnel.

It is worth noting that some of the discussions on mechanisms are based on the results of animal experiments. The manifestation and mechanisms in humans may exhibit some differences, especially factors related to the nervous system, psychology, environment, etc. Additionally, testosterone does not only act on the male reproductive system; it is also associated with the female reproductive system. Perhaps under the influence of various EIF mechanisms, the female reproductive system may also exhibit some changes.

Overall, the various mechanisms that cause EIF have an impact on spermatogenesis, and this impact is predominantly negative. In-depth research into these mechanisms can better assist athletes and fitness enthusiasts in maintaining their health and also enhance the professional advice given by medical personnel and fitness coaches.

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Declarations

Ethical Approval Not Applicable.

Competing Interests On behalf of all authors, the corresponding author states that there is no conflict of interest.

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