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Is there a relationship between inflammation and depression in athletes?

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Abstract

Overtraining is a maladaptive state of athlete's body related to the physical, behavioral and emotional condition, occurring when exercise training exceeds the recoverability. The cytokine hypothesis of overtraining promoted in recent years is seen as the prevailing theory explaining the understanding of the overtraining phenomenon. The high level of pro-inflammatory cytokines (IL-6, TNFα, IL-1β) involved in the inflammatory response may strongly influence not only the central nervous system but also the endocrine and immune systems. Moreover, there is a range of factors in athlete's life that appear to increase the risk of depression development, such as psychological and emotional stress associated with sports competition. The aim of this review was to reveal the role of high level of pro-inflammatory cytokines observed in OTS with the possible occurrence of depression symptoms in athletes. Latest findings have shown an important role of the same pro-inflammatory cytokines in the development of depression. The study discusses a potential mechanism responsible for the development of depression in athletes, which may be helpful in the quick diagnosis of depression basis in athletes. Due to the low number of studies concerning depression and inflammation in athletes further research should be conducted.

KEYWORDS: overtraining, depression, cytokines, inflammation, athletes.

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What is already known on this topic?
Although athletes are considered "tough people" they are enormously susceptible to depression symptoms. The pressure related to sport performance and their unhealthy ambitions, with the dysfunction of the immune and endocrine systems, can extremely affect the psyche of athletes. Due to the increasingly diagnosed cases of depression among athletes this study shows how the low-grade, chronic inflammation accompanying the overtraining syndrome may be responsible for the emergence or intensification of depressive symptoms.

Introduction

It would seem that athletes, hardened by tough training, should be immune to depression; however, this disorder is actually very common among athletes and it weakens their physical condition. Especially elite athletes are doubly exposed to stress which may trigger mood disorders. On the one hand, mental stress, loss of self-esteem, personal and team expectations, and on the other hand, disruptions in the serotonin, pro-inflammatory cytokines or neurotransmitter levels affect the central nervous system contributing to the disease. Depression may significantly change athletes' behavior, ruin their career, or even lead to suicidal risks [1, 2, 3].

All athletes want to get most out of their training thus they train very hard. One of the major components of all training programs is the principle of progressive overload implying working beyond a comfortable level. However, there is a fine line between improved performance and deterioration. The efforts to accelerate the training process may lead to the development of overtraining syndrome [4].

Overtraining is a condition when despite intensive training, an athlete's performance declines. In general, overtraining may be defined as a state in which the athlete has been forced by increasing overloads in the training program to the point where resting is no longer adequate to allow recovery. In consequence, overtraining may be responsible for hormonal, immunological, muscular, mental/emotional and other imbalances causing fatigue, depression, injuries, poor performance and many more. Because overtraining can exhibit various signs and symptoms, depending on the individual, it is more often referred to as overtraining syndrome (OTS) [4, 5].

A number of hypotheses exist aimed to explain OTS. However, the most consistent seems to be the cytokine hypothesis of overtraining which stipulates that the main role in OTS development is played by pro-inflammatory cytokines released at the site of inflammation caused by exercise-induced skeletal muscle microtraumas. When sufficient rest is allowed, pro-inflammatory cytokines are helpful in the healing processes, but when the rest after exercise is inadequate, acute inflammation evolves into chronic response resulting in systemic immune response involving many systems in athlete's body, including the central nervous system and the endocrine system [4, 6].

At present, a great deal of evidence indicates that inflammation may play a significant role in the development of depression [7]. Thus, OTS linked to chronic inflammation seems to be one of the causes of mood disorders leading to the development of depression in athletes. The aim of this review was to discuss the role of high level of pro-inflammatory cytokines observed in OTS and possible occurrence of depression symptoms in athletes.

Depression among athletes – causes and symptoms

The competitive athlete is seen as a well-adjusted individual who demonstrates considerable vigor and well-being. Thus, it would seem that they should be immune to mood disorders, anxiety, fatigue or depression. Besides, well-trained athletes often exhibit a special kind of personality – strongly goal oriented – and perfectionism. However, the strenuous lifestyle packed with sporting events and high expectations may increase the risk of depression [3].

The latest research has suggested that the prevalence of depression among elite athletes is higher than what has been previously reported in the literature. Being ranked among the very elite is related to increased susceptibility to depression, particularly in relation to failed performance [8].

Depression is characterized as a mental health disorder that interferes with physical and physiological well-being. The disorder affects an individual's thoughts, feelings, physical health, behavior and ability to function in everyday activities [9].

There are many different types of depression caused by a variety of factors interacting with one another. Most likely depression is caused by a combination of genetic, biological, environmental and psychological factors. The latter affecting athletic performance include negative thoughts, sense of loss, and sense of failure or stress associated with sport participation, such as excessive anxiety, frustration, fear and many more [10]. Besides, these athletes are also vulnerable to the environmental pressure focused on achieving progress and winning. Due to the hard training athletes are at risk of imbalances in many signal factors responsible for body's well-being, such as hormones, neurotransmitters, cytokines or growth factors. Their disturbances are also identified as potential triggers of depression (Figure 1) [4, 9]. There is also another extremely important problem regarding depression and injury in athletes: they may become depressed after an injury, but in reverse order depression can increase a risk of injury and, in consequence precede, an injury [2, 8].

It is difficult to specify and describe all the symptoms of depression that may occur in athletes and it is not the goal of this paper. However, it should be mentioned that most common signs and symptoms are present across many psychological disorders (Table 1). None of these symptoms is indicative of a mental health problem, but the need for evaluation increases with the number of signs and symptoms reported or observed in athletes [3].

It has to be stressed that at present little is known about the prevalence of depression or other mental

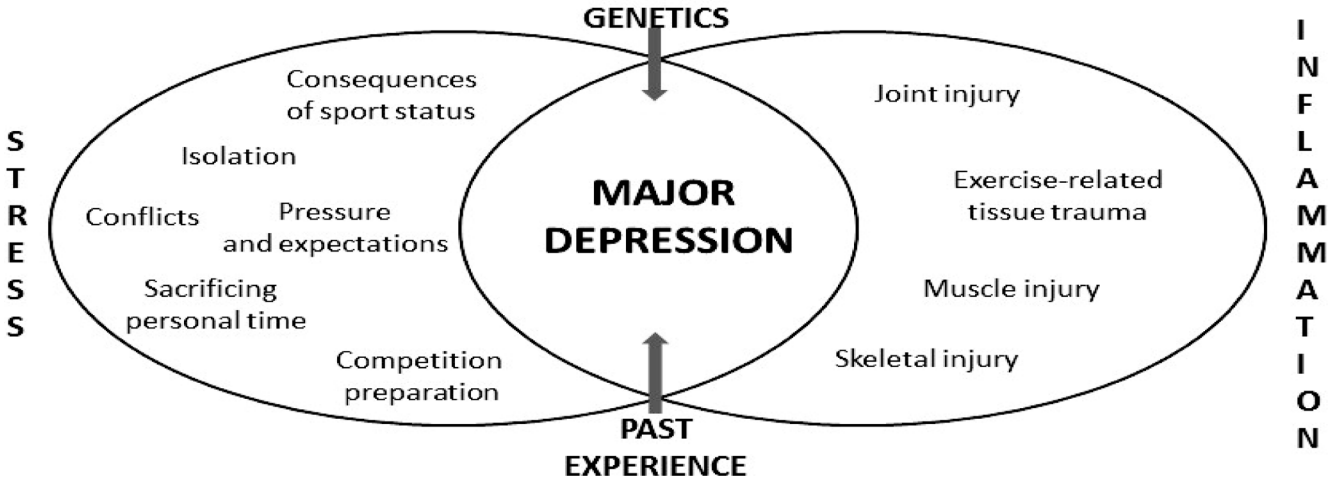

Figure 1. Potential interactions between inflammatory processes, combined with acute and chronic stressors with contribution from psychiatric genetics and past emotional experience (modified after 37, 38)

Table 1. Psychological signs of overtraining and the overtraining syndrome (3)

Symptoms of depression			
Behavioral	Cognitive	Emotional/Psychological	Physical/Medical
Disruption of daily activities	Suicidal thoughts	Feeling out of control	Sleep difficulty
Social withdrawal	Poor concentration	Mood swings	Change in appetite and/or weight
Irresponsibility, lying	Confusion/difficulty making decisions	Excessive worry/fear	Shaking, trembling
Legal issues, fighting, difficulty with authority	Obsessive thoughts	Agitation/irritability	Fatigue, tiredness, weakness
Decrement in sport performance	All-or-nothing thinking	Low self-esteem	Gastrointestinal complains, headaches
Substance use	Negative self-talk	Lack of motivation	Overuse injuries

disorders among athletes. It is a topic of increasing interest, but empirical data is still rare [8, 11] and most of it has emerged in recent years. Moreover, this data indicates a different origin of depression in athletes, emphasizing that further research should be carried out to explain the increasing number of depression episodes among athletes, with special attention given not only to the injured one, but also to those who ended their carriers. The results of empirical research are alarming. Studies carried out among German elite athletes have indicated an overall prevalence of 15% for depression among elite athletes (n = 99). Moreover authors have shown correlations between high levels of depressive symptoms and high levels of chronic stress, negative coping strategies, and negative stress-recovery states. Recent data has also revealed that in long-distance runners, after 6-month endurance training, an increase in depressive symptoms was observed. Furthermore, they were correlated with the function of immune system suggesting that there are relationships between neutrophil functions and mental condition in elite athletes [11]. According to Gulliver et al. [12] 46.4% of studied Australian elite athletes were experiencing symptoms of at least

one mental health problem, 27.2% had symptoms of depression, whereas injured athletes had even higher levels of these symptoms. Not only may current athletes experience problems with depression or depression symptoms, but also the termination of the sporting career is a significant event in athlete's life, and it can be highly distressing leading to depression. According to Wylleman et al. [13] athletes after retirement may experience both depression and depression syndromes such as identity crises or eating disorders. Also Didehbani et al. [14] showed that aging retired athletes have more symptoms of depression compared to controls. Authors also suggested that the number of self-reported concussions may be related to later depressive symptomology, in particular, to cognitive symptoms of depression. Furthermore, data has shown that psychological reactions to injury may play an important role in athletes' depression. It is hard to say how common depression is among injured athletes because of limited data, but it was estimated that among 343 male athletes from a variety of sports 51% had some symptoms of depression after being injured, and 12% became moderately to severely depressed [15]. Research on the emotional responses of athletes to injury shows that depression may be profound and may last a month or more, paralleling athletes' perceived recovery. The association between the injury and depression was also shown by Strain et al. [16]. In their study the relationships between traumatic brain injury and depressive injury occurred during the investigation of retired NFL players, and the results showed that depression after brain injury may be manifested years after injury and it is associated with changes in white matter integrity.

It should also be emphasized that there are strong differences in psychopathology between men and women demonstrating that many sex-based differences reported in the general population apply to elite athletes. According to Schaal et al. [17] 20.02% of female athletes had at least one psychopathology (eating disorder, depression, sleep problems) as opposed to 15.1% in men. And a depression episode was also reported more often in women than in men (4.9% vs 2.6% in the last six months, 16.3% vs 8.7% in a lifetime, accordingly). Authors also indicated the relationships between depression incidences and type of practiced sport. The frequency of minor and major cases of depression were the highest in esthetic sports and aiming/fine motor skills sports.

An extreme example of a consequence of depression in athletes is suicide. Data has indicated that suicide or suicidal ideations and intents are more often found in injured athletes. The sad fact is that depression with suicidal intents is also diagnosed in very young athletes [2, 18].

Trauma-induced inflammation, cytokines, and overtraining syndrome

Skeletal muscle adaptation to athletic training generally involves application of progressive overloads, which implies workload beyond a comfortable level. It is now widely accepted that training and competing result in degrees of microtrauma to muscle, connective tissue, and bones and/or joints. This type of injury was referred to as an adaptive microtrauma (AMT) suggesting micro-injury and regeneration as normal progression associated with training, and is integral in the restoring of homeostasis at an alternate level [17]. The reason for referring to muscle micro-injury as adaptative is that AMT results in a mild inflammatory response with the final purpose of healing. However, the positive end of this type of exercise-induced trauma will be observed only when an appropriate training program is used, with the rest days, hard and easy work days, and/or cross-training included to allow the recovery [4, 19].

However, the same musculoskeletal-joint trauma is proposed as the underlying cause of the overtraining syndrome. It was suggested that such injury might be due to a progression from the initial benign AMT-stage to a subclinical injury in the athlete who is training too hard and too frequently [4].

It has been proven that exercise-induced mechanical trauma results in inflammatory response in both untrained [20] and highly trained elite athletes [21, 22]. The primary focus of acute inflammation is healing, a process crucial to survival. The capacity of muscles to regenerate relies primarily on a specific population of muscle stem cells called satellite cells. However, the overall response is characterized by movement of fluids, plasma proteins and leukocytes from the circulation into the injured tissue. Many of the initial events, manifested within a few hours after the injury, are directed towards local recruitment of specific white blood cells named inflammatory cells. The greatest role in this process is played by neutrophils and monocytes/macrophages. Neutrophils represent the first wave of infiltrating cells. They predominate

during the initial phase of acute inflammation, but after twenty-four hours they are no longer active. Moreover, inflammatory cells produce many cytokines, inflammatory mediators, growth factors or damage signals that have a crucial impact on the behavior of satellite cells during the repair process. In response to these signals, satellite cells are activated and begin to proliferate, thus, in consequence, new myofibers are formed [4, 23]. However, the inflammatory response has to undergo a series of carefully regulated stages to ensure an efficient restoration of tissue homeostasis, and one of the most important factors responsible for the coordination and amplifications of numerous aspects of inflammation is a group of molecules known as cytokines [24].

Cytokines released at the site of local inflammation integrate systemic inflammatory events. They can act in an autocrine manner, affecting the behavior of the cell that releases the cytokine, or in a paracrine manner, affecting the behavior of adjacent cells. Some cytokines may act in an endocrine manner affecting the behavior of distant cells although this depends on their ability to enter the circulation and on their half-life. Cytokines can affect almost every tissue, organ and gland in the body. Moreover, most cytokines have a very wide spectrum of effects, that is, each cytokine has multiple functions [pleiotropy] and also many different cytokines have the same functions [redundancy] [25].

Cytokines are produced and released mainly by immune system cells beside the active muscles, and by a variety of tissues such as adipose tissue and endothelial cells. These molecules may display two kinds of activity: pro-inflammatory such as IL-1b,

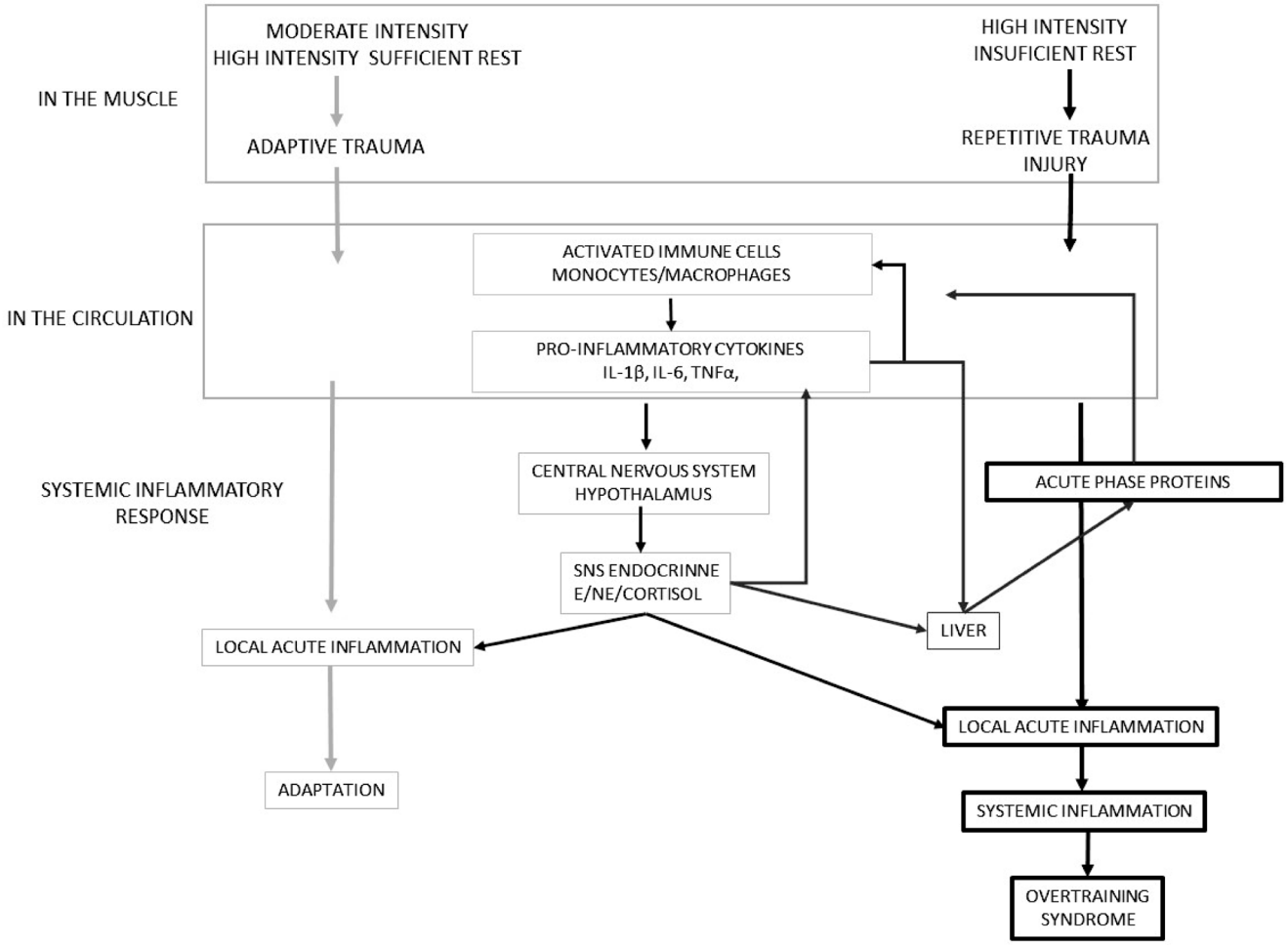

Figure 2. The role of pro-inflammatory cytokines in adaptation and overtraining syndrome development in athletes (modified after 47). E – *epinephrine*; NE – *norepinephrine*

TNFa, IL-6; or anti-inflammatory, for example, Il-6, IL-10, IL-4, IL-5. Among them IL-6 deserves special attention as its role in the pro- and anti-inflammatory balance is that of inflammatory modulator which has also the ability to activate energy pathways to support this process [26, 27].

Cytokines are signaling molecules responsible for intercellular inter-organ and inter-system communication allowing different systems to be informed about the injury in a specific tissue. They enable the influx of white blood cells that participate in tissue regeneration. Moreover, muscle tissue injuries induced by exercise can signalize through the action of cytokines other tissues such as brain, liver, kidney, endothelium, immune cells and endocrine system, especially the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonads axes to promote the combined action required to heal the injury [28, 29].

A number of hypotheses have been proposed to explain the mechanism of overtraining syndrome, yet none has sufficiently accounted for all of the various symptoms associated with OTS. The latest research has been focused on the cytokine hypothesis, which suggests that trauma to the muscular, skeletal and joint systems may be responsible for both the initiating and perpetuating cause of OTS. Moreover, this hypothesis proposes that repetitive trauma to the musculoskeletal system, due to high intensity/volume training, coupled with insufficient recovery time is the predominant cause of overtraining. The cytokine hypothesis of OTS also suggests that many physiological, behavioral and psychological signs and symptoms associated with OTS may occur in the presence of an injury. The connection between the injury and OTS is a release of cytokines at the site of inflammation. With continued high-volume/intensity training without adequate recovery time, a local acute inflammation becomes chronic and cytokines released in this process activate monocytes in circulation which produce large quantities of pro-inflammatory cytokines, resulting in a systemic inflammation. This inflammation is proposed as the central support of OTS (Figure 2) [4, 6].

The most important cytokines, which play a central role in the proposed OTS theory, are inflammatory agents such as IL-1β, TNFα, and IL-6. Locally they are responsible for activation of endothelial cells of local blood vessels stimulated to produce diverse cytokines. Moreover, they may act in the liver to regulate the synthesis of acute phase proteins. Furthermore, IL-1β, TNFα may also act in multiple areas of the brain, where the presence of their receptors has been proven [25, 30]. Recently, a large amount of data has demonstrated that the plasma concentration of pro-inflammatory cytokines increases during and after muscular exercise. Although, TNFα and IL-1β have traditionally been understood as main inducer cytokines of the acute phase of inflammation, the results of studies have led to two main conclusions. After short-term exercise the circulating concentration of these cytokines is either unchanged following exercise, or exhibits relatively small, delayed increments [31]. On the other hand, it has been proven that the tissue trauma after excessive long-term exercise may lead to the development of chronic increases in key proinflammatory cytokines, which results in chronic immune system activation manifested as a systemic inflammation [32].

The other cytokine involved in OTS is IL-6. It is mainly produced after the initial synthesis of IL-1β and TNFα, and it is the chief stimulator of the production of most acute phase proteins. In normal conditions, IL-6 orchestrates the acute response suppressing the level of proinflammatory cytokines without compromising the level of anti-inflammatory cytokines. The anti-inflammatory effects of IL-6 are also demonstrated by the finding that IL-6 stimulates the production of the other anti-inflammatory cytokines. But in chronic diseases, typically exemplified by immune stressors, such as tissue trauma, IL-6 switches its activity as proinflammatory cytokines, and acute inflammation may turn into chronic/systemic that includes an immune response. Literature data have shown that the IL-6 level may increase 100-fold in the circulation during physical exercise, but less dramatic increases are more frequent. Generally, the peak of IL-6 is reached at the end of the exercise or shortly after it and the magnitude of the exercise-induced increase in plasma is determinate by a combination of mode, intensity and duration of exercise. In the beginning it was commonly thought that the exercise-induce growth in IL-6 was a consequence of an immune response due to local damage in working muscle, but more recent works have clearly demonstrated that the contracting skeletal muscle per se is also a large source of the IL-6 in the circulation in response to the exercise [27, 31, 33]. IL-6 is a multi-functional cytokine that regulates a variety of physiological events such as cell proliferation, differentiation, survival or cell apoptosis. As a major messenger molecule, IL-6 plays also an

important role in the immune, the endocrine, and the nervous systems and in bone metabolism. Moreover, IL-6 has been implicated in the pathology of different diseases including depression [34].

Chronic inflammation, cytokines and depression

To be beneficial, the inflammatory reaction must be acute, destroying injuries agent within a short period of time and in a localized area. However, when the activation of the inflammatory response is altered or prolonged, it can actually cause more damage to a host than the pathogen itself. It is now widely recognizable that chronic inflammation plays a part in autoimmune disorders, asthma, obesity, and other medical morbidities [35].

During recent years, it has been established that pro-inflammatory cytokines induce not only symptoms of sickness, but also true major depressive disorders in physically ill patients with no previous history of mental disorders. Some of the mechanisms that might be responsible for inflammation-mediated sickness and depression have now been elucidated. These findings suggest that the brain-cytokine system is an unsuspected conductor of the ensemble of neuronal circuits and neurotransmitters that organize physiological and pathological behavior [36].

In the past two decades the number of studies linking psychiatric illnesses to inflammatory processes has been growing. Most of them have risen from an attempt to link these illnesses to a particular major depressive disorder with changes in body homeostasis triggered by a combination of stress factors and changes in immune/inflammatory pathways to cause changes in the brain structure and function [7].

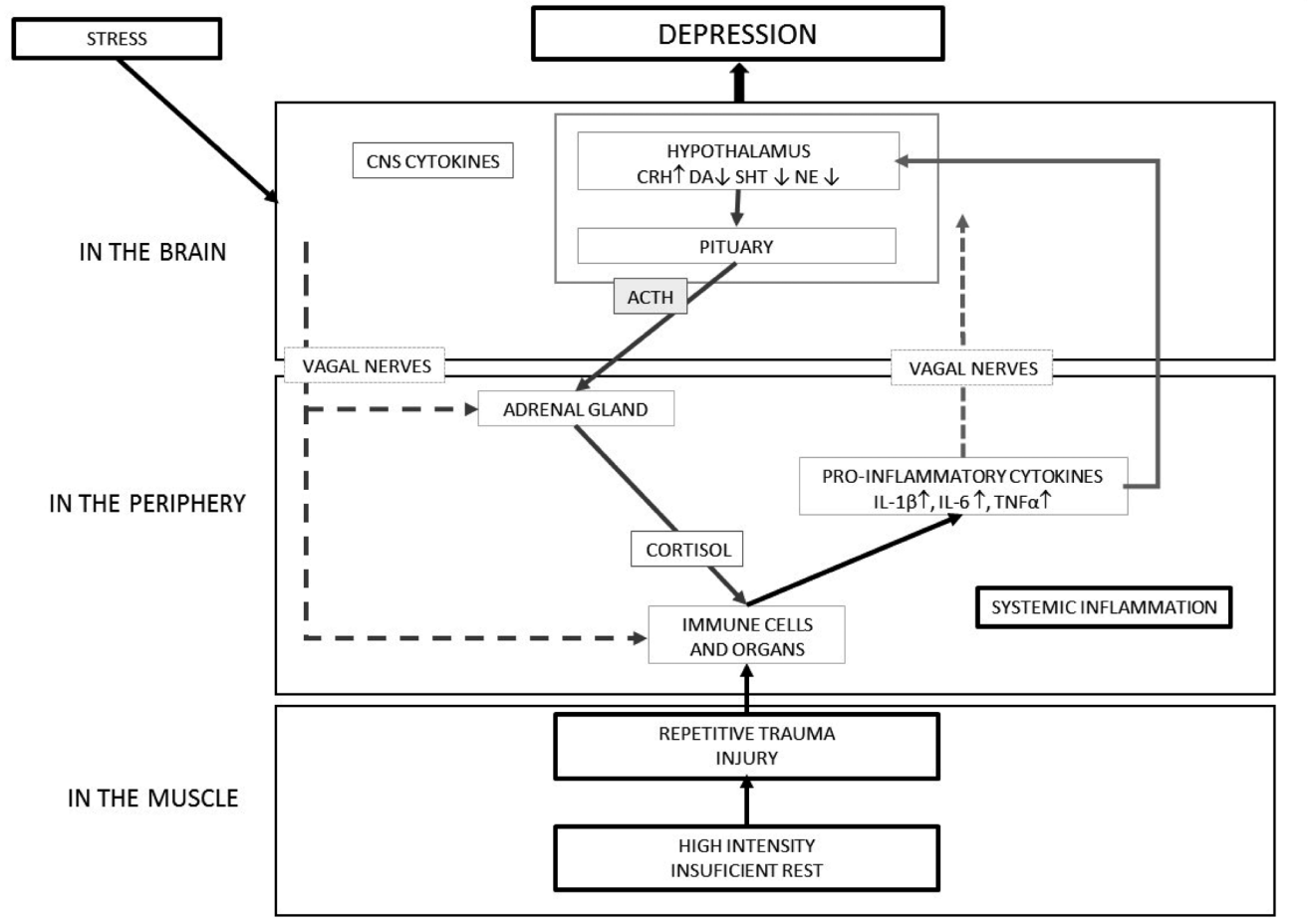

Figure 3. Brain – immune interactions and implications caused by muscle tissue trauma and systemic inflammation (modified after 38, 47). CNS – *central nervous system*; CRH – *corticotropin-releasing hormone*; DA – Dopamine; STH – *somatotropin*; NE – *norpeinephrinei*; ACTH – *adrenocorticotropic hormone*

Without a doubt athletes, especially elite and champions, are under strong pressure. They experience not only lifestyle or emotional stress, but, above all, they are influenced by training and competitive stress. It has been proven that a certain amount of stress is beneficial for athletes; however, too much stress has a direct effect on hormonal balance and may also affect the immune system or the entire metabolism. There are a lot of factors which can increase stress and anxiety in athletes involved not only in psychological stress such as fear of competition, but also stressors associated with training, nutrition, lifestyle or health. According to athletes exposed to the effects of hard training the role of the acute and chronic immune and inflammatory processes should be stressed as one of major factors causing depression [37, 38].

The immune-cytokine model of depression is an entirely new concept in the understanding of the riddle of depression. This model views depression to be any number of chronic physical-biological disorders with mental-emotional symptoms. The basis of this model is greater than the normal amount of various cytokines secreted during chronic immune system activation [39].

Cytokines are considered a main factor of the immunological basis of depression since they provoke a wide spectrum of neuropsychiatric symptoms. The main evidence that links inflammation and depression comes from the observation of elevated levels of inflammatory markers in patients with depression along with the findings that inflammatory medical illnesses are associated with greater rates of major depression. In addition, people who are treated with inflammatory substances (interferons, cytokines) start to show depression-like symptoms. Moreover, the dose-dependent relationship between level of cytokines and severity of depression was observed [40, 41]. Data have shown that concentrations of a number of inflammatory markers including cytokines, chemokines, and acute phase reactant proteins can be found in patients with depression. Among them the most replicated findings concern elevated levels of pro-inflammatory cytokines such as TNF-α, Il-1β, and Il-6 [42].

Pro-inflammatory cytokines circulating in the periphery do not freely cross the blood-brain barrier, but are hypothesized to signal the brain via vagal and trigeminal afferent nerves, specific transport mechanisms and gaps in the barrier such as circumventricular organs and choroid plexus [38]. Moreover, the brain owns the cytokine network that is made up of cells (neurons and glial elements) that not only produces cytokines and express cytokine receptors, but also amplifies cytokine signals. The CNS cytokine network can mirror the peripheral immune response by producing pro-inflammatory cytokines and prostaglandins which in turn can have profound effects on neurotransmitter and CRH function as well as on behavior (Figure 3) [36, 38].

Increased production of pro-inflammatory cytokines in the brain is responsible for alterations in the metabolism of serotonin, norepinephrine and dopamine in brain regions essential to the regulation of emotions including the limbic system as well as the regulation of psychomotor function and reward, which results in behavioral changes observed in depression [38].

The high level of pro-inflammatory cytokines responsible for the systemic inflammation is also the cause of hyperactivity of hypothalamus-pituitary-adrenal axis. HPA axis activity is governed by the secretion of corticotrophin releasing hormone (CRH) from the hypothalamus, which in turn activates the secretion of andrenocorticotrophin hormone (ACTH) from the pituitary. ACTH then stimulates the secretion of glucocorticoids (cortisol) from the adrenal cortex [38, 43]. The cytokine signal transduction pathways are also able to disrupt glucocorticoid receptor signaling and thus may contribute to altered glucocorticoid-mediated feedback regulation of both CRH and further pro-inflammatory cytokines release [38].

However, it should be noted that athletes' immune and nervous systems must handle not only physical stressors such as muscle trauma or injury, but also accumulation of psychological stressors (mental and emotional) [44].

Psychological stress is a common risk factor for the development of major depression. Increasing data indicate that psychological stress activates pro-inflammatory cytokines including Il-1, Il-6 and TNF and their signaling pathways in the periphery and central CNS. Chronic stress, among others, exerts the effects on the hypothalamus as well as the brain stem. In response, the HPA axis is activated, but the sustained stress may lead to HPA axis "fatigue" and to blunting its functions. Long-term stress also causes glucocorticoid-resistance which results in a decline of immune the system's sensitivity to cortisol. Long-lasting chronic stress is also responsible for activation of the inflammation related transcription

pathway resulting in increases of the pro-inflammatory cytokines which may induce or enhance inflammatory response (Figure 3) [45].

There is data concerning overtrained athletes with changes in their global mood/behavior/cognition. This pattern varies considerably among athletes and may reflect not only individual heterogeneity, but, in fact, it may be related to the type of training. For example, anaerobic training may lead athletes to experience a greater degree of anxiety/agitation, whereas endurance training may be responsible for a greater degree of depression [4, 6].

Morgan et al. [46] reported that up to 80% of athletes with OTS had significantly elevated levels of psychological depression. It has also been hypothesized that highly motivated athletes, consumed with the will to perform well and win, became frustrated by poor performance that may be caused by inadequate recovery during overreaching and overtraining. Next, frustration leads to increased practice time and training volume and intensity, which results in less regeneration, increased fatigue, and reduced performance [9].

Conclusions

This review summarizes two current theories: cytokine hypothesis of overtraining and immune-model of depression, and discusses their potential role in the development and expression of depressive symptoms in athletes. Certainly this set of hypotheses is unlikely to explain the development of all instances of depression in athletes, but at least it supports the possibility of existence of a specific pathway in athletes and a link between muscle tissue trauma, OTS syndrome, and depression.

Overtraining syndrome and an involved progressive cycle of decline is actually a result of molecular changes evoked by muscle microtrauma and lack of sufficient rest time needed for full regeneration and recovery. In this condition, a local acute inflammation may evolve into chronic inflammation and, in consequence, produce systemic inflammation. A systemic immune response involves the CNS, liver, and immune system. An increased level of pro-inflammatory cytokines may activate the sympathetic nervous system and HPA axis, thus the disturbances in blood levels of catecholamines and glucocorticosteroids are observed. Pro-inflammatory cytokines are also responsible for the increased level of acute phase proteins produced by the liver. According to the latest research, the high level of pro-inflammatory cytokines has also been responsible for the progression of depressive symptoms. Because athletes are at higher risk of disturbances in inflammatory mediator levels and the prevalence of systemic inflammation according to OTS, there is also a high risk of depression occurrence.

However, both depression and OTS are a very pleomorphic and heterogeneous phenotype thus this review presents only one of the possible mechanism of depression development in athletes. There is an urgent need to identify potential inflammatory factors and their correlation to quality evidence linking these factors with the risk of development of depression in athletes, especially when inflammation is one of the mediating pathways to an increased risk of occurrence of depression in overtrained athletes.

What this paper adds?

Although athletes are considered "tough people" they are enormously susceptible to depression symptoms. The pressure related to sport performance and their unhealthy ambitions, along with dysfunctions of the immune and endocrine systems, can extremely affect the psyche of athletes. Due to the increasing number of diagnosed cases of depression among athletes this study shows how the low-grade, chronic inflammation accompanying the overtraining syndrome may be responsible for the emergence or intensification of depressive symptoms.

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