THE IMPACT OF EXERCISE TRAINING IN THE TREATMENT OF DRUG ADDICTION. THE ROLE OF CHANGES IN NEUROTRANSMITTERS

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ABSTRACT

Background. Dopamine and serotonin including are among neurotransmitters involved in addiction to drugs such as the methamphetamine, which suffered cause major damage. This study aimed to investigate the effect of exercise training in the treatment of drug addiction with respect to the changes in neurotransmitters).

Methods. In this study, English and Persian databases including Magiran, SID, Google Scholar, PubMed and Scopus were searched, using keywords such as Exercise, Neurotransmitter, Health Treatment and Patient Addiction. Related articles published during 1986–2017 were assessed. Prevalence of depression in diabetic patients, as well as the relationship between depression and different variables including age, sex, and marital status, was evaluated. This study presents a review of research that has examined the effects of exercise training on drug addiction.

Results. Regular physical activity as aerobic and resistance training resulted in a significant increase in circulatory levels of serotonin and dopamine.

Conclusion. Based on the results achieved by literature analysis and reliance on its major findings it can be concluded that physical activity and exercise training can have an effect on the circulatory levels of both neurotransmitters, such as serotonin and dopamine in addicted people to drugs, and it can also be a helpful factor with respect to the considerations in the treatment of addiction and as well as physical and mental improvement of addicted people.

Keywords: addiction, exercise, health, neurotransmitter, treatment.

INTRODUCTION

Addiction is a chronic disease that requires long-term treatment. Drugs have been used to reduce the intake and prevent the return to drugs, but these methods were not suitable (Hosseini, Alaei, Naderi, Sharifi, & Zahed, 2009). Most addicts tend to change the drug-dependent lifestyle, but there are many problems in the treatment phase that cause recurrence and withdrawal from the treatment period (Ravndal & Vaglum, 1998). For this reason, addiction has been introduced as an acute and reversible problem (van den Brink & Haasen, 2006). Unfortunately, the main problem in the treatment of addicts, even in the long term of cleanliness, is their high rate of relapse (Yan & Nabeshima, 2009). Also, the withdrawal of treatment and re-use of drugs is associated with more negative consequences, such as the likelihood of high consumption of drugs, greater dependence on substances, the use of various drugs, increased criminal behavior and the imposition of additional costs on health and treatment networks (Veilleux, Colvin, Anderson, York, & Heinz, 2010). Drug abuse also affects the body's systems, including the respiratory system and the cardiovascular system, but most of its work has been observed to be mostly effective on the central nervous system, the auto nerve and the digestive system (Le Moal & Koob, 2007). Drug abuse damages the normal functioning of the brain reward cortex (Gardner, 2011). In the early stages of addiction, when the of drug use begins, dopamine in the reward path (for example, the nucleus accumbency, abdominal tangent area and the cerebral cortex) creates incentives for drug use (Koob & Volkow, 2010). Drug use, including psychostimulants, alcohol, nicotine, hallucinogens, cannabinoids and opiates, the amount of dopamine in the nucleus accumbens has increased (Yoshimoto, McBride, Lumeng, & Li, 1992). Blocking this pathway can disrupt the prescription of drugs in particular psychological stimuli (Chang, Sawyer, Lee, & Woodward, 1994).

Drug abuse is a disease that caused by affecting the brain and, the behavior and disorder in several central neurotransmitters. The most important of these systems are dopaminergic and serotonergic systems. Knowledge about the activities of neurotransmitters and proprietary affected by the drug can help treatment (Giannini & Slaby, 1989). Dopamine is produced at the dopaminergic axon terminal (Sadock, Sadock, & Levin, 2007), which has a very important role in controlling motivation, learning positive and negative things, choosing actions for good things and avoiding bad things (Bromberg-Martin, Matsumoto, & Hikosaka, 2010), regulating movement, feeling, cognitive motivation and feeling of enjoyment (Greenwood et al., 2011). Dopamine function also ends with two general ways of reabsorption and decomposition. Serotonin is a monovalent neurotransmitter that is synthesized in gastric mucosal membrane cells and central nervous system cells in the presence of tryptophan, an essential amino acid species. This hormone plays an important role in the regulation of the nervous-hormonal system, mood modification, appetite, sleep, physiological activity, and effective cognitive activity in learning and memory. Serotonin is stored after being produced inside the germs until it is released by the action potential of the neuron. The synaptic effect of serotonin ends up through its reabsorption into the presynaptic terminal by the carrier molecule in the plasmid membrane (Sadock et al., 2007). Physical activity, and in particular, sports training, has the ability to can be used in both the first and final stages of the addiction process as a non-prescriptive adjuvant therapy and has secondary health properties (for example, prevention of obesity and secondary diseases such as diabetes). Physical activity and sports activate the same system in the brain that drugs use achieved through the increase of dopamine and its receptors (Greenwood et al., 2011). These effects may also be helpful in reducing the effects of drug abuse and reducing the vulnerability of drug use (Guezennec et al., 1998). Increasing physical activity or exercise training is accompanied by a decrease in cardiovascular disease and type 2 diabetes, high blood pressure, some cancers, and in general, the decrease of death risk (Kraus, 2010). Regular aerobic exercise like continuous or intermittent walking can decrease the weight (Alizadeh et al., 2013; MJ & MA, 2011). Resistance exercise can also decrease body fats and modify the risk factors (Tresierras & Balady, 2009). Endurance exercise leads to some physiological adaptations, such as the increase of oxidative enzymes, capillary density, the number of mitochondria, maximal aerobic power and the efficiency of cardiovascular system (Tarpenning, Hawkins, Marcell, & Wiswell, 2006). In contrast, resistance exercise can lead to the increase in muscle mass, adaptive proteins and accordingly the increase in muscle strength (Portegijs et al., 2008). When doing long-term aerobic exercises, big muscular masses are used, but when doing resistance exercises, more body parts are involved and it seems that the effects caused by them are different. It has also been shown that resistance exercises and the increase in muscle mass can increase the responses to blood glucose (Braith & Stewart, 2006). Strength enhancement is a result of simultaneous *recruitment* of more motor units, which causes modification of the contraction and increases the ability of muscle to generate force. Training has the ability of increasing the preventive impulses or even opposing it and it can allow the muscle to gain higher levels of strength. Therefore, it is possible to gain strength through decreasing nervous inhibition (Issurin, 2005). Moreover, another strength generating factor is the contact levels of actin and myosin cross bridges. The higher the contact in the cross bridges, the more the level of strength can increase (Luo, McNamara, & Moran, 2005). Endurance increase occurs by the increase in capillary density, the concentration of muscle myoglobin, the number and size of mitochondria and the oxidative enzymes in the body. One of the most important adaptations of endurance exercise is the increase in capillaries surrounding each muscle fiber (Hermansen & Wachtlova, 1971). Endurance exercise increases the number of muscle fibers in any muscle and certain cross-sectional area of muscle. Therefore, blood flow in the muscles, gas exchange, waste materials and nutritious materials increase. These changes are accompanied by adaptations to the oxygen delivery system, which causes the improvement in the oxidative system and endurance (Smith & Fernhall, 2011). Therefore, the purpose of this study was to investigate the effect of exercise training in the treatment of drug addiction from the standpoint of changes in neurotransmitters.

METHODS

The present study was conducted in search of texts in Persian and English informational databases such as Magiran, Google scholars, SID, PubMed Scopus, with the keywords of exercise, neurotransmitter, health, treatment, addiction related to 1986 to 2017. It is focused on the effects of exercise on drug addiction treatment in the aspect of changes in neural mediators. These neural mediators include serotonin and dopamine. All the studies that were not focused specifically on the effects of exercise and drug addiction (from a neural mediator changes point of view) were entirely omitted. The study looks at research on the effects of exercise training on drug addiction in the human and animals with focusing on the neurotransmitter. The findings of the articles are presented in a table with a summary of human and animal research on the effects of various exercises and training on neurotransmitters and addiction-related factors in drug addicted individuals and animals.

RESULTS

Based on our search, eight human studies on the effects of different exercises on neural mediators and the factors affected by drug addiction in addicts and also 12 animal studies on the effects of various exercises on neural mediators and the factors affected by drug addiction in addicted animals done between the years 1986 to 2017 were applied in this study. All the studies which were not specifically focused on the effects of exercise and treatment of drug addiction (from the neural mediator aspect) were omitted from the present study. Reviewing the studies on the effects of different exercises and training on neurotransmitters and factor influenced by addiction in human and animals, regular physical activity as an aerobic and resistance training can lead to significant increases in circulatory levels of serotonin and dopamine (Table 1 and 2).

Components of a workout:

A) Warm-up: At least 5–10 minutes of relaxation and stretching exercises (mostly static stretching exercises).

B) Training: At least 20–60 minutes aerobic, resistance and combination training with frequencies of 2 to 3 sessions per week.

C) Cool-down: At least 5 minutes of static stretching or low-intensity respiratory cardiac activity (such as walking).

The warm-up phase should include at least 5–10 minutes of static stretching and relaxation along with slow running. Warm-up is a transitional period that allows the body to adapt to the physiological, biomechanical and bioenergy conditions required during exercise. Also, warm-up expands the range of motion and can reduce the risk of injury. If the goal is to increase cardio-respiratory endurance, aerobic exercise, sports or resistance training, especially in long-term or repetitive activities, it is best to start with dynamic cardio-respiratory activity in the warm-up phase and then stretching movements. The main activity phase should include aerobic exercise, resistance, flexibility, or sports activities. After the training period, the cool-down period begins, which includes light and slow aerobic activity and stretching (with a pause) for 5–10 minutes. The goal is to cool-down, gradually recover heart rate, blood pressure, and removals of byproducts and metabolites when performing the main activity (Ferguson, 2014; Garber et al., 2011).

DISCUSSION

Amphetamine or cocaine can release normal neurotransmitters too much or prevent the normal recycling of chemicals in the brain. This disruption creates a very intensive message and ultimately the communication paths get disordered (Ahmadi et al., 2005). Consistent use of narcotic drugs by stimulating compromising mechanisms creates short-term and lasting changes in the function of neurons and opioid-sensitive neural networks. Creating tolerance, dependence and sensitivity are examples of compromise mechanisms (Williams, Christie, & Manzoni, 2001). These changes make the addicted people stay vulnerable many years after discontinued use (Nestler, 2001). These enduring changes in the brain and the interaction of opioid drugs and synaptic formability in various brain regions contribute to the onset of recurrence

Table 1. **Summary of animal studies on the effects of various training on neurotransmitter and addiction related factors**

Authors (years)	Title of study	Subjects	Type of exercise or training	Results
1. Chaouloff, Laude, & Merino (1986)	Amphetamine and α-methyl-p-tyrosine affect the exercise-induced imbalance between the availability of tryptophan and synthesis of serotonin in the brain of the rat.	Rat	Run	Control of 5-HT synthesis in the brain with the availability of tryptophan is altered during exercise, and the increased activity of central catecholamines is effective in such a change. The activity of dopamine in the brain can affect brain serotonin responses during exercise. In this study, there was a large amount of dopamine in areas where serotonin levels increased.
2. MacRae et al. (1987)	Endurance training effects on striatal D 2 dopamine receptor binding and striatal dopamine metabolite levels.	Rat	6 months of endurance training	Exercise can modify a number of DA sites and DA metabolism in young adult animals. Aerobic exercises increased dopamine levels. The concentration of dopamine DA and D2 in young runners increased significantly.
3. Dey, Singh, & Dey (1992)	Exercise training: significance of regional alterations in serotonin metabolism of rat brain in relation to antidepressant effect of exercise.	Rat	one hour high intensity swimming and long-term exercise (4 weeks swimming, 6 days per week)	An acute exercise session increased serotonin levels in the brain stem and hypothalamus, but did not alter serotonin levels in the cerebral cortex and the hippocampus, while long-term exercise increased serotonin levels in all areas of the brain, and one week after all the last exercise session was still intact.
4. Bequet et al. (2001)	Changes caused by aerobic exercise on glucose and serotonin of brain through microdialysis probes in the hippocampus of rats; combined effects of glucose.	Rats	Aerobic exercise	During the exercise, synthesis and metabolism of noradrenalin, serotonin and dopamine increase and are applicable in treatment of disease with lack of dopamine. These results show that exercise significantly changes the level of serotonin which was modified dramatically through injecting glucose.
5. Cosgrove, Hunter, & Carroll (2002)	Decreased self-administered cocaine in the model of running the mice: sex differences	Rat	Run	A model of voluntary running in mice and possibly voluntary exercise in humans may be a substitute for the reduction of drug abuse as a natural reward.
6. Langfort et al. (2006)	The effects of endurance exercise on local metabolism of serotonin in brain during the first level of detraining in female rats.	Female rats	Six weeks of endurance training	The increased of serotonin caused by aerobic exercises was reported.
7. Vučcković et al. (2010)	Exercise elevates dopamine D2 receptor in a mouse model of Parkinson's disease: in vivo imaging with [18F] fallypride.	Rat	Treadmill	As a result of aerobic training, the levels of dopamine increased.
8. Lynch et al. (2010)	Aerobic training reduces cocaine search behavior and related neuronal compatibility in the cerebral cortex.	Rat	Aerobic training	Exercise training the same system in the brain, which seeks to consume drugs like cocaine through increased dopamine and its receptors. Therefore, exercise can be a protective way of preventing the return to drug use and can result in neuro-hormone compliance.
9. Alberghina et al. (2010)	Reponses of peripheral serotonergic to exercise in horses.	Six horses	Aerobic exercises	Aerobic exercise increases the level of serotonin
10. Fontes-Ribeiro et al. (2011)	May exercise prevent addiction?	Rats adult male	Continuous training include a treadmill running with increase intensity for eight weeks	Physical training according to a specific daily schedule can prevent amphetamine addiction in similar situations used in this study.
11. O'dell et al. (2012)	Effect of exercise on the improvement of damage caused by methamphetamine uses on dopaminergic and serotonergic terminals.	Amphetamine addicted mice	Seven days exercise	They concluded that 7 days of exercise in mice caused significant changes in the serotonin and dopamine levels and their receptors in the brain.
12. Goekint et al. (2012)	Sprinting stimulates dopaminergic neurotransmission in rats but shows no effects on brain-derived neurotrophic factor.	Rats	60 minutes of running on treadmill	The level of dopamine increases due to aerobic exercises.

Table 2. **Summary of human studies on the effects of various training on neurotransmitter and addiction related factors**

Authors (years)	Title of study	Subjects	Type of exercise or training	Results
1. Valim et al. (2013)	The effects of aerobic and stretch training on the level of serum serotonin (5HT) and its primary metabolite (5HIAA).	22 women	Aerobic (walking) and stretching exercise	The significant increase in the level of 5HT and 5HIAA caused by aerobic exercises.
2. Vafamand et al. (2013)	The effect of eight weeks aerobic training on serotonin and dopamine levels.	30 addicted people	Aerobic training	Regular aerobic training affected the levels of serotonin and dopamine in addicted women and increase cardio respiratory endurance.
3. Robertson et al. (2015)	The effect of exercise training on D2 / D3 receptors in methamphetamine users during behavioral therapy.	19 addicted people	3 days a week, 8 weeks of exercise	Exercise can increase the amount of dopamine in the experimental group.
4. Arazi et al. (2016)	The effect of training on blood serotonin and dopamine levels and physical fitness factors of opium addicts in rehabilitation period.	34 addicts to opium	Aerobic exercise is usually 2 to 3 sessions per week and each session is 20 to 30 minutes walking exercise	Training is small but regular and walking can increase serotonin and dopamine levels.
5. Arazi et al. (2016)	Aerobic training can increase serotonin levels.	20 people addicted to methamphetamine	Eight weeks aerobic training	The effect of 8-week aerobic training on plasma serotonin levels and the depression rate of methamphetamine addicted men in rehab.
6. Arazi et al. (2017)	Changes in blood levels of endorphins, serotonin and dopamine and some physical health variables following a period of aerobic training on men with a history of methamphetamine addiction.	30 people addicted to methamphetamine	Eight weeks aerobic training	Aerobic training can significantly increase blood serotonin, dopamine and endorphins level.
7. Dadvand et al. (2017)	Effect of a course of aerobic training on blood serotonin and endorphins levels and reduction of depression among drug addicted women.	30 drug addicts	Eight weeks aerobic training	Aerobic exercises can increase levels of serotonin and endorphins.
8. Arazi et al. (2017)	Neurotransmitters and cardiovascular responses to aerobic and resistance training in methamphetamine addicts.	10 people addicted to methamphetamine	Aerobic and resistance training	Aerobic and resistance training can significantly increase blood serotonin and dopamine levels.

Table 3. **Recommendations based on aerobic training**

FITT- VP	Recommendations
Frequency	• Equal or more than 5 days per week, moderate intensity exercise, or equal to or more than 3 days per week of intense activity, or a combination of moderate to intense exercise that is equal to or greater than 3-5 days per week is recommended.
Intensity	• In most adults, moderate or high intensity is recommended. • In untrained people, low to moderate activities are recommended.
Duration	• 30-60 minutes a day of activities moderate targeted, or 20-60 minutes per day of intense exercise, or a combination of moderate to intense exercise in a day is recommended in most adults. Exercise less than 20 minutes per day can be beneficial, especially in people who have been inactive.
Type	• Regular and targeted activities that performed with large muscles groups are continuous and rhythmic.
Volume	• The target volume is equal to or greater than 500–1000 set-minutes per week recommended. • Increase the number of steps taken, equal to or more than 2000 steps per day to achieve the daily step equal to or greater than 7000 steps per day is useful. • In people, who are not interested or those who cannot reach the recommended amount of activity, doing less exercise can be helpful.
Pattern	• A exercise is conducted on a day-to-day basis (continuously) or in equal periods more than 10 minutes per day to reach the duration and amount of the desired exercise.
Progress	• Gradual progress in the amount of exercise, frequency and severity (to maintain) the achievement of the intended exercise is acceptable.

Note. Ferguson, B. (2014). ACSM's Guidelines for Exercise Testing and Prescription 9th Ed. 2014. *The Journal of the Canadian Chiropractic Association, 58*(3), 328; Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I.-M., . . . Swain, D. P. (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Medicine and Science in Sports and Exercise, 43*(7), 1334–1359.

Table 4. **Recommendations based on resistance training**

FITT - VP	Recommendations
Frequency	• Each major muscle group should be given 2-3 times per week.
Intensity	• Severity of 1-RM 60–70% (moderate to high intensity) to increase strength in beginners and moderately active people. • 1RM intensity 40–50% (very low to low) to increase strength in beginner elderly. • The severity of the 1-RM 40–50% (very low to low) may be beneficial for improving the strength of the beginner's limb, which begins the resistance training program. • Intensity below 1-RM 50% (low to moderate intensity) to increase muscle endurance • 1-RM intensity (20–50%1RM) for increased power in elders.
Duration	• No specific training period has been identified for the effectiveness of the workout.
Type	• Resistance exercises are recommended with the main muscle groups. • Multi-articular exercises that affect more than one muscle group and on the muscles that support and antagonists are recommended in adults. • Single-jointed exercises that involve the original muscle groups can also be included in the resistance training program, typically following multiple muscle exercises of the particular muscle group. • You can use various sports equipment or body weight to do movements.
Repetitions	• 8–12 repetitions recommended for increasing the strength and power of most adults. • 10–15 repetitions recommended for beginners to increase strength and power in middle-aged and elderly people. • 15–20 repetitions are recommended to increase muscular endurance.
Sets	• 4 sets in most adults is recommended to increase strength and power. • Single sets can be particularly effective in beginners and elderly people. • Equal or more than 2 sets are effective in increasing muscle endurance.
Pattern	• The rest intervals are 2–3 minutes between sets of repetitions. • For each muscle group, interval intervals equal to or greater than 48 hours between sessions are recommended.
Progress	• Progressive resistance or more repetitions at any time or increase in the number of sessions is recommended.

Note. Ferguson, B. (2014). ACSM's Guidelines for Exercise Testing and Prescription 9th Ed. 2014. *The Journal of the Canadian Chiropractic Association, 58*(3), 328; Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I.-M., . . . Swain, D. P. (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Medicine and Science in Sports and Exercise, 43*(7), 1334–1359.

Table 5. **Recommendations based on flexibility training**

FITT- VP	Recommendations
Frequency	• Equal to or more than 2–3 sessions per week; • Stretching exercises are more effective every day.
Intensity	• Stretching to the point of feeling tight or slight (pain threshold)
Duration	• In most adults, static stretching is advisable for 60–30 seconds. • In adult carriages, stretching for 30–60 seconds can have some benefits. • In the case of PNF stretching, 3–6 seconds of light-to-moderate intensity contraction (for example, 20–75% maximum voluntary contraction) followed by 10–30 seconds of auxiliary stretching.
Type	• For each major tendon muscle group, a series of flexible exercise is recommended. • Static stretching (for example, active or inactive), dynamic, ballistic, and PNF stretching are effective.
Volume	• A reasonable goal is to perform a total of 60 seconds of stretching for each stretching exercise**.**
Pattern	• It is recommended to repeat each stroke for 2–4 times. • Flexural activities are effective when the muscle is accompanied by aerobic exercise with low to moderate intensity.
Progress	• Desirable progress is not fully understood.

Note. Ferguson, B. (2014). ACSM's Guidelines for Exercise Testing and Prescription 9th Ed. 2014. *The Journal of the Canadian Chiropractic Association, 58*(3), 328; Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I.-M., . . . Swain, D. P. (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Medicine and Science in Sports and Exercise, 43*(7), 1334–1359.

(Nestler, 2002). Exercise is one of the effective and cost-benefit methods of addiction. There is a lot of evidence that voluntary sports have self-motivated effects by influencing reward systems (Lett, Grant, Koh, & Smith, 2001). Recent experiences and clinical findings have shown that long-term regular exercise can activate the central opioid system and stimulate endogenous opioid release while increasing the threshold of pain in both humans and animals (Koyuncuoğlu, Nurten, Enginar, & Özerman, 2001). Exercise can be a useful tool in the prevention and treatment of drug dependence (Ehringer, Hoft, & Zunhammer, 2009). Some well-known molecular mechanisms of voluntary exercise include increased neuronal growth, thirst and dendritic growth, the number of presynaptic vesicles, increased neuronal factor derived from the brain, and expression of most genes involved in synaptic plasticity in the hippocampus and Cortex of the brain (Cotman & Engesser-Cesar, 2002). Drug abuse is a major hygiene and health problem that has many social and economic consequences. Commonly used drugs that are being misused include psychotic stimuli such as cocaine, amphetamines and their derivatives. Although it has already proven that mesoporticolimbic dopamine plays a major role in the behavioral responses resulting from the use of these drugs, which includes enhancement and refinement effects, recent studies indicate the involvement of the brain serotonin system in relation to drug abuse (Adlard & Cotman, 2004). Psychosocial stimuli not only inhibit dopamine delivery and increase dopamine release but also inhibit serotonin reuptake and increase it in extracellular space (Filip, Alenina, Bader, & Przegaliński, 2010). Repetitive drug use causes prolonged damage to dopaminergic and serotonergic terminals and reduces serotonin, dopamine, and their synthesis enzymes (Giannini et al., 1989). Exercise, on the other hand, also reduces the damage to monoaminergic terminals (dopamine and serotonin) and increases their levels in the blood. This correlation shows that exercise can have many behavioral and physiological benefits for improving addicted people (O'dell, Galvez, Ball, & Marshall, 2012). There is a relationship between dopamine and all aspects of behavior, such as motor activity, and it has been proven that exercise increases the release and synthesis of dopamine, stimulates neoplasm, improves health, and feels good (Morgan & Malison, 2007). Drug abuse such as amphetamine leads to an increase in the reaction between oxygen, nitrogen and damage to monoammonergic venereal terminals (Fontes-Ribeiro, Marques, Pereira, Silva, & Macedo, 2011). On the other long-term exercises increase the activity of endogenous antioxidant enzymes (Segura-Aguilar & Kostrzewa, 2004). Therefore, aerobic training in this study may be effective in increasing serotonin and dopamine levels. In prolonged aerobic exercises, free tryptophan is increased in plasma and enters the brain cells, which results in the synthesis of serotonin and its distribution in the bloodstream (O'dell et al., 2012). Another mechanism that increases serotonin and dopamine is a neurotrophic growth factor. Aerobic exercise induces an increase in in vivo endothelial growth factor and may contribute to injuries due to angiogenesis stimulation and a direct effect on the neurotrophic growth factor, which leads to the reconstruction and repair of damaged terminals of monoammonergic dopamine and serotonin (Morgan et al., 2007). Evidence suggests that short-term and long-term exercises lead to changes in many neurotransmitter systems (Lynch, Peterson, Sanchez, Abel, & Smith, 2013).

Accordingly, physical activity and exercise are used as a contributing factor in the treatment of drug use disorders and the improvement of the status of addicted people (Zschucke, Heinz, & Ströhle, 2012). In their study, Chaouloff et al. (1987) concluded that brain dopamine activity could be effective on brain serotonin responses during exercise. In this study, a large amount of dopamine was observed in the areas where serotonin levels increased (Chaouloff et al., 1987).

The effects of endurance training on the binding of astryatal dopamine D2 receptors and the levels of dopamine stearate metabolites were investigated by MacRae, Spirduso, Cartee, Farrar, and Wilcox (1987). This study examined the effects of six months of endurance training on young adults on the relationship between the uniformity of D2 levels and its metabolite in stratium and the dependence and concentration of dopamine DA and D2 in the samples. The dopamine DA and D2 concentrations of young runners significantly Increased (MacRae et al., 1987).

Dey, Singh, and Dey (1992) investigated the effect of a swim and a long-term exercise (4 weeks swimming, 6 days a week) on serotonin levels in different brain regions. An acute exercise session increased serotonin levels in the brain stem and hypothalamus, but did not alter serotonin levels in the cerebral cortex and hippocampus, while long-term exercise increased serotonin levels in all areas of the brain and one week after the last sporting session remained the same (Dey et al., 1992). Bequet, Gomez-Merino, Berthelot, and Guezennec (2001) investigated the changes caused by aerobic exercises on glucose and serotonin of the brain received by microdialysis probes in rats' hippocampus. It was observed that in the first minute of exercise the amount of serotonin changes by glucose alterations, but it follows a different pattern during the resting time and after 30 minutes of rest, and the level of serotonin increases to the maximum level. These results show that exercise training changes the level of serotonin which is dramatically modified by glucose injection (Bequet et al., 2001). Cosgrove, Hunter, and Carroll (2002) showed that a model of voluntary running in mice and possibly voluntary exercise in humans could be a substitute for reducing drug abuse (Cosgrove et al., 2002). In another study, Langfort et al. (2006) examined the effects of endurance training on tryptophan and serotonin and the main acid metabolism in different parts of female rats' brain, at the end of the last training session and 48 hours after that. Endurance exercises were done for six weeks and finally the results showed an increase in serotonin level due to aerobic exercises (Langfort et al., 2006). Vučcković et al. (2010) showed that aerobic training increased dopamine levels. Lynch et al. (2013) showed that exercise activated the same system in the brain that seeked to consume narcotics such as cocaine by increasing dopamine and its receptors (Lynch et al., 2013). Therefore, exercise can be a protective way to prevent the return to substance use and cause hormonal neurological adaptation (Vučcković et al., 2010). Alberghina, Giannetto, and Piccione (2010) conducted a study to determine the effects of exercise on plasma tryptophan and blood free serotonin in six healthy horses. The findings showed that aerobic exercises can cause the increase in serotonin levels (Alberghina, Giannetto, & Piccione, 2010). Fontes-Ribeiro et al. (2011) aimed to investigate the effect of exercise in the mechanism of amphetamine addiction in experimental rats on adult male rats. The results of the study showed that regular exercise overlaps with drug abuse, for this reason, the effect of exercise on the dopaminergic system and a change in dopamine is observed (Fontes-Ribeiro et al., 2011). O'dell et al. (2012) examined the effect of exercise on improving the damage of serotonergic terminals in addicted mice and concluded that exercise training in rats caused significant changes in serotonin levels and their receptors in brain regions (O'dell et al., 2012). Goekint et al. (2011) reported that high-speed running stimulates dopaminergic neurotransmission in rats' hippocampus, but does not affect BDNF. The purpose of the aforementioned study was to investigate the effect of sprint exercise training on monoaminergic neurotransmission and BDNF. The results showed that 60 minutes running increased dopamine secretion in rats' hippocampus (Goekint et al., 2011). Also, in a study by Valim et al. (2013), aerobic and stretch training increased serum serotonin (5HT) and its primary metabolite (5HIAA). Vafamand, Kargarfard, and Marandi (2012) investigated the effect of eight weeks of aerobic training on serotonin and dopamine levels in 30 addicted women in Isfahan Central Prison. The results indicated that aerobic training significantly increased serotonin and dopamine levels in the experimental group compared to the control one (Vafamand et al., 2012). Robertson et al. (2016) aimed to investigate the effect of the training program on the amount of dopamine research on addicted men and women. The study showed that exercise increases can the amount of dopamine in the experimental group (Robertson et al., 2016). Arazi, Mollazadeh, Dadvand, and Davaran (2016) conducted a study to investigate the effect of exercise on serum levels of blood serotonin and dopamine and the physical fitness factors of opium addicts during rehabilitation course (Arazi et al., 2016). In another study, the effect of seven weeks of combined exercise (aerobic-resistance) on blood levels of serotonin and dopamine and physical fitness factors on men who were addicted to methamphetamine in the rehabilitation period. The researchers concluded that training increased dopamine and serotonin levels in the experimental group (Arazi, Damirchi, & Poulab, 2016). Arazi and Dadvand (2017) investigated the effects of eight weeks of aerobic training on plasma serotonin levels and the rate of depression of men methamphetamine addicts in the rehabilitation period. The results indicated that aerobic exercise significantly increased serotonin levels in the experimental group compared to controls (Arazi & Dadvand, 2017). Another study conducted to investigate the changes in blood levels of endorphins, serotonin and dopamine and some physical health variables following a period of aerobic exercise training on men with a history of methamphetamine addiction.

Finally, the results of the study showed an increase in serotonin, dopamine and endorphin levels after eight weeks of aerobic exercise (Arazi, Rafati, & Dadvand, 2017). Dadvand and Daryanoosh (2017) investigated the effect of a course of aerobic training on serotonin and endorphin levels and depression of drugs addicted women in 30 drugs addicted women. The results of this study showed that aerobic training can increase blood serotonin and endorphin levels in the experimental group compared to control (Dadvand & Daryanoosh, 2017). The effects of aerobic and resistance training on neurotransmitters and cardiovascular responses, investigated by (Arazi, Dadvand, & Fard, 2017). The results of the study showed an increase in blood serotonin and dopamine levels after aerobic and resistance training (Arazi et al., 2017).

CONCLUSION

In summary, based on the findings of controlled animal and human studies, it was determined that exercise training with increasing activity of endogenous antioxidant enzymes and neurotrophic growth factors can lead to reconstruction and repair of damaged terminals of monoaminergic dopamine and serotonin. It suggests that these training can help with the improvement of physical and hormonal status along with drug therapy and can be useful as a complementary therapeutic mechanism through effective mechanisms that can promote and improve health. Therefore, in order to increase the neurotransmitters level of serotonin and dopamine, addicts can perform these type of training (aerobic, resistance, and flexibility) with considerations during treatment.

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