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Effect of Swimming Training in Addiction Withdrawal Period on Thyroid Hormones in Addicted Rats

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Abstract

Introduction: Today, drug use is increasing in the world. Physiological changes in the body are one of the most important consequences of drug use; one of the most important of these changes is the hormonal changes in the body. Therefore, the purpose of this study was to investigate the effect of swimming training in addiction treatment on thyroid hormones in methadone addicted rats.

Methods: Rats were randomly divided into seven groups, including: (1) eight weeks of swimming training, (2) eight weeks of methadone consumption, (3) eight weeks of swimming training with methadone, (4) four weeks of methadone and four weeks of non-methadone consumption, (5) four weeks of methadone and four weeks of swimming training, (6) four weeks of swimming training with methadone and four weeks of swimming without methadone, and (7) control. The swimming training consisted of three sessions per week and each session was 30 minutes. Also, methadone was injected daily at 2 mg / kg body weight of methadone peritoneally. Blood samples were collected 24 hours after the last training session. For analysis of data, Kolmogorov-Smirnov test and one way analysis of variance (ANOVA) were used ($p \leq 0.05$).

Results: Eeight weeks of swimming training, eight weeks of methadone consumption, eight weeks of swimming training with methadone and also four weeks of swimming training during methadone withdrawal period had no significant effect on thyroxine ($p = 0.29$), triiodothyronine $p= 0.06$) and thyroid stimulating hormone ($p = 0.24$) in rats.

Conclusion: Eight weeks of swimming training, methadone consumption, swimming practice along with methadone and also four weeks of swimming training during methadone withdrawal period have no significant effect on thyroid hormones in rats.

Key words: Swimming, Methadone, Addiction, Thyroxine, Triiodothyronine, Thyroid Stimulating Hormone

Introduction

Drug addiction is undoubtedly one of the biggest problems for human societies, with governments spending a lot of their budget each year fighting it (1). In this context, some of the synthetic or semi-synthetic materials can exert different effects, including weakening, stimulation, or hallucinations in the central nervous system (2). In general, any substance that changes the mental, psychological, and emotional state of the body's natural function is called the drug. The consequences of the use of these substances can bring about behavioral and cognitive changes as well as physiological changes in the body, where in hormonal changes are of particular importance (3). The thyroid gland synthesizes thyroxine or tetraiodothyronine hormones, triiodothyronine and calcitonin by the gland, and these hormones are controlled

by the thyroid stimulating hormone. One of the functions of thyroid hormones is to increase the rate of base metabolism, body temperature, protein synthesis, body sensitivity and response to catecholamine, and regulation of metabolism (4). It has been shown that continuous intake of some medications may affect thyroid function, for example, opium and its derivatives, due to their effects on intestinal movements and interference with iodine intake, their effects on the liver and interference with metabolism, or direct effects on the thyroid and the pituitary may cause thyroid function impairment. For instance, the presence of some common clinical symptoms such as weight loss and muscle weakness in drug addicts and people with some thyroid dysfunction has sparked this issue (5). Research has shown that morphine consumption can reduce the activity of the hypothalamic-pituitary axis (6). A group of researchers reported a decrease in thyroid stimulating hormone levels and a lack of changes in triiodothyronine and thyroxine during morphine use (7). In a study, it was reported that opium addiction in rats could increase thyroid stimulating hormone levels and decrease thyroxine levels, and generally affect the function of the thyroid gland (8). Although it is thought that drug use may change thyroid function, its precise mechanism is still not well defined (9- 11). In the studies, it was found that swimming practice improves the symptoms of knee osteoarthritis in rats, support for heart tissue in rats against diabetes-induced oxidative stress, elevated vascular endothelial growth factor of the kidney (12), and no significant change in the concentration of metallothionein in the liver of rats (13). It was also found that regular swimming exercise induced decreased morphine dependency in rats (14) and antinociceptive effects in morphine dependent mice following withdrawal syndrome (15), and treadmill exercises reduced the dependence of addicted animals (16). In the case of thyroid hormones, a study showed that sound stress inhibited the secretion of thyroid hormones in rats (17). In another study, the use of Portulaca oleracea increased thyroid hormones in rats (18). There is evidence to suggest that exercise has encouraging effects on laboratory animals that these stimulatory effects are mediated through the androgenic opioid system (16), and it has been shown that exercise activates some organs of the body that are affected by morphine and other opiates (19). Research results about the effect of exercise on thyroid hormones are not the same, so that various studies have shown that exercise can cause increase, decrease or no change in thyroid hormone levels (20, 21, 22). In our studies, we did not find any research of the effects of swimming practice on addiction withdrawal on thyroid hormones (thyroxine, triiodothyronine and thyroid stimulating hormone), so the present study seeks to answer the question whether eight weeks of methadone consumption has a significant effect on thyroid hormones thyroxine, triiodothyronine and thyroid stimulating hormone? Also, can swimming training impact the effects of methadone on thyroxine, triiodothyronine, and thyroid stimulating hormone in rats?

Methods

In this experimental study, adult male rats, Sprague Dawley, who were proliferated at the Animal Breeding Center in Marvdasht Islamic Azad University, were used. Animals were transferred to the animal holding room at sport physiology research center of Marvdasht Islamic Azad University at an environmental temperature of 22 to 27 degrees Celsius, controlled light (12-hour light and dark cycle), and eight-day adaptation period. Animals' access to water and food was free during the period. In this study, totally 84 rats were tested. The onset of experimental interventions included a training program and methadone consumption after the eight-day adaptation period. Rats were randomly assigned to seven equal groups of 12 rats, including (1) eight

weeks of swimming training, (2) eight weeks of methadone consumption, (3) eight weeks of swimming training combined with methadone, (4) four weeks of methadone and four weeks No methadone intake, (5) Four weeks of methadone and four weeks of swimming training, (6) four weeks of swimming training with methadone and four weeks of swimming training without methadone and (7) control. The swimming training and the combination of swimming training with methadone were given three days a week for swimming (30 minutes for swimming in a swimming tank) (23). Also, methadone and methadone treatment groups combined with swimming training received 2 mg /kg per day for methadone peritoneally (24, 25).

The study period was eight weeks. After this time, blood sampling was performed to measure the variables studied. Before blood collection, animals were kept fasting for 16 hours. After blood collection, 5 cc blood was injected into the Falcon tubes (for measuring thyroid hormones). Blood samples without EDTA were kept at laboratory temperature for 40 minutes and then centrifuged for 15 minutes to prepare serum with 3000 rpm. It should be noted that the duration of treatment was eight weeks, in which the first four weeks was of physical dependence. During the course of treatment, in all groups except the 7th group at the end of the fourth and eighth week, 30 minutes after the last dose of methadone to ensure the addiction of methadone to the rats and the occurrence of withdrawal symptoms, the naloxone (5 mg / kg) was injected peritoneally. After injection, the symptoms of withdrawal syndrome were evaluated in rats. The naloxone animals were placed in a mirror chamber for 30 minutes and their behavior was evaluated. After naloxone injection, the rats began to develop withdrawal symptoms such as diarrhea, teeth chattering, abdominal stretching and ptosis (26, 27). The swimming training protocol presented the way that the rats swam in the swimming tank for 30 minutes and at the end the body of rats were dried by special hair dryers (28). It should be noted that in each swimming tank only five rats were swallowed. 24 hours after the last training session, at the end of the eighth week, the rats were sacrificed to measure the parameters in order to assess the biochemical changes induced by the effects of swimming training and methadone consumption.

Blood sampling was done by first anesthetizing the animals with 10% ketamine (50 mg / kg) and xylosin 2% (10 mg / kg) after about 5 minutes. The blood vessel chest was then opened straight from the left ventricle of the animal. After transferring blood samples to the laboratory for examination of thyroid hormones, 10 samples were lost because of lack of proper transportation by the expert. Their number in the eight weeks of swimming training was 1 sample, four weeks of methadone and four weeks of non-administration Methadone 4 samples, four weeks of methadone consumption, and four weeks of swimming training, 2 samples, four weeks of methadone and swimming training, and four weeks of swimming without methadone, 1 sample and control of 2 samples.

It should be noted that all ethical and legal aspects of this research have been confirmed and approved in the Sport Physiology Laboratory of Islamic Azad University, Marvdasht Branch. The collected data were analyzed using SPSS software, statistical tests of Kolomogrov Smirnov and one way analysis of variance ($p \leq 0.05$).

Results

The weight of the rats in the seven groups of research is presented in Table 1, and the levels of thyroid hormones are presented in Table 2. Regarding the normal results of the Kolmogorov-Smirnov test, the results of the one-way analysis of variance analysis in Table 3 showed that there was no significant difference in thyroxine levels ($p = 0.29$), triiodothyronine ($p = 0.66$) and thyroid stimulating hormone ($p= 0.24$), so eight weeks of swimming training, eight weeks of

methadone consumption, Eight weeks of swimming training with methadone and also four weeks of swimming training during methadone withdrawal period have no significant effect on thyroxine, triiodothyronine and thyroid stimulating hormone in rats.

Table 1. Description of weight of rats in seven groups of research (standard deviation ± mean)

Group	Weight (g) in post test	Weight (g) in pre-test
Eight weeks of swimming training	231.00±22.64	185.71±19.15
Eight weeks of methadone consumption	218.30±25.10	195.07±24.67
Eight weeks of swimming training with methadone	210.07±17.19	195.30±17.58
Four weeks of methadone and four weeks of non-methadone consumption	229.45±30.75	190.36±25.44
Four weeks of methadone and four weeks of swimming training	209.78±25.10	196.14±26.92
Four weeks of swimming training with methadone and four weeks of swimming without methadone	210.30±30.14	195.30±26.33
Control	214.28±18.04	178.42±19.60

Table 2. Levels of thyroxine, triiodothronine and thyroid stimulating hormone in the study groups (standard deviation ± mean)

Variable / Group	Thyroid stimulating hormone (mu / L)	Triiodothyronine (mg / dl)	Thyroxine (: mg / dl)
Eight weeks of swimming training	0.04±0.01	0.57±0.06	45.88±6.05
Eight weeks of methadone consumption	0.03±0.01	0.65±0.06	49.90±4.48
Eight weeks of swimming training with methadone	0.03±0.01	0.64±0.09	49.48±6.75
Four weeks of methadone and four weeks of non-methadone consumption	0.05±0.01	0.67±0.07	52.77±4.95
Four weeks of methadone and four weeks of swimming training	0.04±0.02	0.63±0.08	49.25±5.38
Four weeks of swimming training with methadone and four weeks of swimming without methadone	0.03±0.01	0.59±0.05	47.98±6.70
Control	0.04±0.01	0.63±0.07	48.52±5.39

Table 3. One-way analysis of variance of thyroid hormones levels in the research groups

Variable	Statistics	Sum of squares	df	Mean of squares	F	p
Thyroxine	**Between groups**	241.26	6	41.21	1.23	0.29
	Within groups	2232.73	67	33.32		
	Total	2480.00	73			
Triiodothronine	**Between groups**	0.06	6	0.01	2.08	0.06
	Within groups	0.36	67	0.005		
	Total	0.43	73			
Thyroid stimulating hormone	**Between groups**	0.003	6	0.001	1.35	0.24
	Within groups	0.02	67	0.001		
	Total	0.02	73			

Discussion

The results of this study showed that four and eight weeks of methadone consumption increased thyroxine and triiodothyronine levels and decreased thyroid stimulating hormone, but these changes were not statistically significant. Different studies have been done on thyroid hormones such as thyroxine, triiodothyronine and thyroid stimulating hormone that have contradictory results, so that the results of some researches are consistent with the results of this research. For example, in a study that examined the effects of cigarette smoking and hookah (hubble-bubble) on changes in the levels of triiodothyronine, thyroxine and stimulating hormones in male rats, the results showed that smoking of cigarette or hookahs can induce increasing thyroid function (29- 31). Also, beta-endorphin, morphine, and heroin (32) reduce thyroid stimulating hormone levels in rats, or in addicts T3 increases (33, 34). On the other hand, the research results of some researchers are not consistent with the results of this study. The results showed that heroin use reduced T3 and T4 levels (32), or did not change T4 levels (35). Or due to the use of opium in male and female addicted rats, T4 and TSH significantly decreased and increased, respectively; however, T3 did not show a significant change, and it can be said that opioid addiction affects the function of thyroid gland (8). In another study, chronic morphine consumption reduced thyroxine and triiodothyronine and did not alter thyroid stimulating hormone levels (36). In this vein, chronic nicotine use in mice has been shown to reduce the activity of the thyroid gland (37). Perhaps the lack of consistency is due to the dosage, the time of injection, the drugs used in some co-investigations and the type of feeding of the mice. The decrease in TSH can be attributed to the inhibitory effect of opioids on the pituitary gland, and since some of the inhibitory effects of opioids on TSH have not been detected in the non-thyroid mice, this effect can be attributed to the reinforcement of negative feedback from thyroid hormones on

the pituitary by opioids (8). Probably methadone can specifically enhance activating some of the enzymes present in the T3 and T4 pathways, which can increase the amount of these two hormones. In the T4 synthesis pathway, known as the coupling reaction, the two molecules are joined together to form the T4. It is possible that methadone will affect this stage and increase T4, but the same applies to T3 (8). In addition, the results of this study showed that eight weeks of swimming training reduced the amount of thyroxine and triiodothyronine and did not alter the thyroid stimulating hormone, which this reduction is not statistically significant. The results of some studies are consistent with our findings. So that aerobic exercises (70 % of maximum heart rate) have been shown to reduce the level of triiodothyronine (22). Or they reported a reduction in thyroid hormones after exercise (38, 39). On the other hand, the findings of some other studies are not consistent with the findings of this study. For example, it was found that aerobic exercises (70% of maximum heart rate) increase thyroxine levels and thyroid stimulating hormone (22), or that intense exercise increase thyroid hormones (40). Also, regular exercise increase T3, T4, and TSH significantly (41). The lack of consistency is likely to be due to the duration of activity, the type of activity and the time taken for blood samples. It has now been accepted that exercise is useful in the treatment of drug dependence, although the mechanism of exercise in the treatment of dependence has not been determined, much emphasis has been placed on the theory of beta-endorphin secretion. In this regard, it has been shown that trained animals use less morphine than the control group (10, 42). Since exercise can activate many neurotransmitter systems involved in the addictive process and increase the release of endorphins (43), it is likely that this way it is able to neutralize the effects of methadone and reduce thyroid hormones. Aerobic exercise increases the release of β-endorphins and other intraperitoneal opioid peptides, resulting in inducing the effects of morphine and other non-invasive pseudoephedrating receptors, and, in this way, it can reduce the severity of symptoms during the withdrawal period and hence, be useful in the withdrawal process (44). The result of a study found that regular swimming training could reduce morphine dependence in rats (14). Another study showed that treadmill exercise reduced the dependency symptoms in addicted animals (16). Also, the practice of swimming had analgesic effects in morphine-dependent mice following the withdrawal syndrome (15). Swimming exercise, in addition to improving cognitive functions in mice, (45) reduced the response of the pain to Acetic Acid in pain models (46). There is some evidence suggesting that exercise has encouraging effects in experimental animals, which these stimulatory effects are mediated through the androgenic opioid system (16)

It has been shown that exercise activates some organs of the body that are affected by morphine and other opiates (19).

Conclusion

In general, it can be concluded that eight weeks of swimming training, methadone consumption, swimming training with methadone and also four weeks of swimming training during methadone withdrawal period have no significant effect on thyroid hormones in rats.

Ethical issues

No applicable.

Authors' contributions

All authors equally contributed to the writing and revision of this paper.

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References

1. Salehi B, Solhi H, Fotovat A, Motamedi D, Moradi S, Ebrahimi S. The comparison of the psychiatric disorders between opium addicts' families referring to opium withdrawal clinics and non-addicts' families referring to blood transmission centers. Arak Univ Med Sci J. 2012; 15 (3): 32- 38.
2. Aharonovich E, Hasin DS, Brooks AC, Liu X, Bisaga A, Nunes EV. Cognitive deficits predict low treatment retention in cocaine dependent patients. Drug Alcohol Depend. 2006; 81 (3): 22- 313.
3. Herman D, Heinz A, Mnn K. Dysregulation if the hypothalamic pituitary thyroid axis in alcoholism. Addiction. 2002; 97 (11): 1381- 1389.
4. Kim M, Ladenson P. Thyroid. In: Goldman L, Schafer AI, eds. Cecil Medicine. 24th ed. Philadelphia, Pa: Saunders Elsevier, 2011.
5. Wenzel KW. Pharmacological interference with in vitro tests of thyroid function. Metab J. 1981; 30: 717- 732.
6. Hochberg Z, Pacak K, Chrousos GP. Endocrine withdrawal syndromes. Endocr Rev Aug. 2003; 24 (4): 38- 523.
7. Del¬Valle-Soto ME, Iglesias L, Calzada B, Vaga JA, Hernandez LC, Perez-Cass A. Effects of morphine on the pituitary-thyroid axis: morphological and analytical studies. Funct Dev Morphol. 1991; 1 (4): 3- 6.
8. Mami S, Eghbali M, Khosravi A, Purmehdi Brojeni M, Salati A, Mami F, et al . Effect of opium addiction on T4, T3 and TSH in male and female rats. J Ilam Univ Med Sci. 2012; 20 (2): 17- 22.
9. Dietrich JW, Landgrafe G, Fotiadou EH. TSH and thyrotropic agonists: key actors in thyroid homeostasis. J Thyroid Res. 2012; 351864.
10. Hajizadeh Moghaddam A, Mirkarimpour SH, Alizadeh MH, Kordi MR, Fallah-Mohammadi M. Separate and concomitant effect of swimming exercise and quercetin supplementation on rat's knee osteoarthritis. J Isfahan Med Sch. 2014; 32 (288): 1- 13.
11. Farzanegi P, Habibian M, Anvari SM. Effect of swimming training and arbutin supplement oncardiac antioxidant enzymes and oxidative stress in diabetic rats. J Gorgan Univ Med Sci. 2015; 17 (3): 39- 45.
12. Mirdar SH, Jarrahi M, Hedayati M, Hajizade A, Hamidian Gh. Effect of swimming during pregnancy on vascular endothelial growth factor level of neonatal rat kidney tissue. J Gorgan Univ Med Sci.2015; 16 (4): 106- 110.
13. Mirdar Harijani S, Musavi N, Aliasgharzade Oliaei H. The effect of endurance swimming training on liver apoptotic index and metallothioneine concentration in pregnant rats. Daneshvar Med. 2014; 21 (108): 51- 58.
14. Fadaei A, Miladi Gorji H, Makvand Hosseini S. Effects of regular swimming exercises on severity of naloxone-precipitated morphine withdrawal signs in rats. ZUMS J. 2013; 21 (87): 54- 62.
15. Yadgari F, Heidarianpour A, Nazem F. Effects of regular swimming exercise on pain threshold following withdrawal syndrome in morphine dependent rats. Physiol Pharmacol. 2012; 15: 294- 288.
16. Saadipour KH, Sarkaki AR, Badavi M, Alaei HA. Effect of short-term forced exercise on naloxone induced withdrawal symptoms in morphine addicted male rats. Armaghan Danesh J. 2007; 12 (4): 73- 79.
17. Mohammadi S, Ahmadi R, Khakpur B. Combined effects of mobile phone radiation (940 MHz) and noise (100 db, 5700- 700 Hz) on plasma level of the thyroid hormones in rats. Daneshvar Med J. 2015; 22 (118): 51- 60.
18. Changizi Ashtiyani S, Zarei A, Taheri S, Ramazani M. Effect of alcoholic extract of Portulaca Oleracea on serum level of thyroid hormones in hypercholestrolemic

Rats. J Gorgan Univ Med Sci. 2015; 17 (2): 52-58.
19. Hosseini M, Alaei HA, Naderi A, Sharifi MR, Zahed R. Treadmill exercise reduces self-administration of morphine in male rats. Pathophysiology. 2009; 16 (1): 3- 7.
20. Rasaei MJ, Gaeini A, Nazem F. Hormonal adaptation & Sport. 1st ed. Tehran: Tarbiat Modares Publication. 1995; 76- 80.
21. Katarina TB. Exercise endocrinology.1th ed. United States of America: Human Kinetics; 2003: 123- 131.
22. Ciloglu F, Peker I, Pehlivan A, Karacabey K, İlhan N, Saygin O, Ozmerdivenli R. Exercise intensity and its effects on thyroid hormones. Neuroendocrinology Let. 2005; (26): 172- 780.
23. Drumond LE, Mourão FA, Leite HR, Abreu RV, Reis HJ, Moraes MF, Pereira GS, Massensini AR. Differential effects of swimming training on neuronal calcium sensor-1 expression in rat hippocampus/cortex and in object recognition memory tasks. Brain Res Bull. 2012; 88 (4): 385- 391.
24. Jannike M, Andersen Christine F, Olaussen A, Jørg M. Long-term methadone treatment impairs novelty preference in rats both when present and absent in brain tissue. Pharm Biochem Behav. 2011; 98 (3): 412- 416.
25. Agnieszka Z, Ewa T, Dominika N, Adam B, Małgorzata L, Adam P, Irena N. Effects of morphine and methadone treatment on mRNA expression of Gα (i) subunits in rat brains. Pharm Reports. 2010; 62 (6): 1197- 1203.
26. Geoffrey SF, Ling Nancy S, Tappe Charles E. Methadone induced physical dependence in the rat. Life Sci. 1984; 34 (7): 683- 690.
27. Pierce TL, Hope W, Raper C. The induction and quantitation of methadone dependence in the rat. J Pharmacol Toxicol Methods. 1996; 36 (3): 137- 146.
28. Drumond LE, Mourão FA, Leite HR, Abreu RV, Reis HJ, Moraes MF, Pereira GS, Massensini AR. Differential effects of swimming training on neuronal calcium sensor-1 expression in rat hippocampus/cortex and in object recognition memory tasks. Brain Res Bull. 2012; 88 (4): 385- 391.
29. Ahmadi R, Asgary V, Abedi G. The comparison between the effects of cigarette and waterpipe smoke on serum level of TSH, T3 and T4 in male rats. RJMS. 2012; 19 (102): 12- 17.
30. Allan MJ, George AH. The roles of the opioid peptides in controlling thyroid stimulating hormone release. Life Sci. 1982; 31 (22): 2529- 2536.
31. Berglund A, Millard WJ, Gabriel SM, Simpkins JW. Opiate-thyroid hormone Interactions in the regulation of thyrotropin secretion in the rat. Neuroendocrinology. 1990; 52: 303- 308.
32. Bhoir KK, Suryawanshi SA, Pandey AK. Effects of sub-lethal heroin administration on thyroid stimulating hormone (TSH), thyroid hormones (T3, T4) and thyroid gland of Musnorvegicus. J Environ Biol. 2009; 30: 989- 994.
33. Shahsavar F, Ghanadi K, Jafarzadeh M, Nasiri B, Forutani SH. Opium addiction decreases T3 uptake amount. Life Sci J. 2013; 10 (5s): 608- 610.
34. Zhang GF, Tang YL, Smith AK, Liu ZQ, Sheng LX, Chi Y, et al. Alterations in pituitary-thyroid axis function among opioid dependent subjects after acute and protracted abstinence. Addict Biol. 2009; 14 (3): 310- 314.
35. Rasheed A, Tareen IA. Effects of heroin on thyroid function, cortisol and testosterone level in addicts. Pol J Pharmacol. 1995; 47 (5): 441- 444.
36. Khalili Najafabady M, Bagheri A, Hadavandkhani A. Chronic effect of morphine on thyroid glands in male rats. Iran J Endocrin Metab. 2005; 7 (1): 67- 72.
37. Fazelipoor S, Hadipour Jahromi M, Behtash N, Tootiyan Z, Shafie M, Asadi F,

et al. Histological, histometrical and thyroid hormones serum level evaluation after chronic nicotine exposure in mice. Med Sci. 2012; 21 (4): 268- 274.
38. Moore AW, Timmerman S, Brownlee KK, Rubin DA, Hackney AC. Strenuous, fatiguing exercise: relationship of cortisol to circulating thyroid hormones. Int J Endocrinol Metab. 2005; 1: 18- 24.
39. Lehmann M, Knizia K, Gastmann U, et al. Influence of 6-week, 6 days per week, training on pituitary function in recreational athletes. Brit J Sports Med. 1993; 27: 186- 192.
40. Anthony C, Hackney Kallman A, Karen P, Hosick Daniela A, Rubin Claudio L. Thyroid hormonal responses to intensive interval versus steady-state endurance exercise sessions. Hormones. 2012; 11 (1): 54- 60.
41. Bansal A, Kaushik A, Singh CM, Sharma V, Singh H. The effect of regular physical exercise on the thyroid function of treated hypothyroid patients: An interventional study at a tertiary care center in Bastar region of India. Arch Med Health Sci. 2015; 3: 244- 246.
42. Bize R, Johnson JA, Plotnikoff RC. Physical activity level and health-related quality of life in the general adult population: a systematic review. Prev Med. 2007; 45 (6): 401- 415.
43. Sforzo GA. Opioids and exercise .An update. Sports Med. 1989; 7 (2): 109- 124.
44. Jalalvand A, Heidarianpour A, Almasi J. Acute effects of swimming exercise on withdrawal syndrome sign in morphine-dependent rats. J Sabzevar Univ Med Sci. 2013; 20 (3): 373- 379.
45. Rada KZ, Kaneko T, Tahara S, et al. Regular exercise improves cognitive function and decreases oxidative damage in rat brain. Neurochem Intern. 2001; 38: 17- 23.
46. Mazzardo Martins L, Martins DF, Marcon R, et al. High-intensity extended swimming exercise reduces pain-related behavior in mice: involvement of endogenous opioids and the serotonergic system. J Pain. 2010; 11: 1384- 1393.