

Original Research

# The Effect of 8-Weeks of Combined Exercise with Consuming Methadone on Liver Enzymes Levels in Withdrawal Addiction Females

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## Abstract

Due to the increase in the rate of addiction among women; and the importance of the role of parenting and managing for women at home, the importance of health is felt in this stratum by the community and one of the most affecting factors on health is regular exercise. This study aimed to investigate the effectiveness of the 8-weeks combined exercise with methadone on liver enzymes (including: ALT, AST, ALP) in withdrawal addiction females. This semi-experimental study was done at Zahedan addiction Camp on 43 available addicted women divided two groups of methadone (N: 20) and methadone with exercise (N: 23), randomly by the same variables such as age, type and duration of drug withdrawal and body mass index. Levels of liver enzymes were assessed by blood sampling before and after 8-weeks. To compare the means between two groups on the same continuous, independent t-test and to compare two means were from same group (pre test vs. post test) paired t-test via SPSS software version 24 were used. Statistical significant level P was taken to be less than 0.05 ( $P < 0.05$ ). Results showed that the levels of liver enzymes (ALT, AST, ALP) in both groups decreased; which one except ALP in methadone with combined exercise group ( $T = -1.701$ ,  $P = 0.117$ ) all of them were significant ( $P < 0.05$ ). Also, independent t-test showed no significant difference between post-test's levels of AST, ALT, ALP enzymes between methods ( $P > 0.05$ ). This was a good pilot study upon which it might want to use a more robust study by the bigger sample size to detect more and various findings and from the new technological aspects it suggests that combination exercise (aerobic + strength training) could be a new useful way to use with consuming methadone at withdrawal addiction females probably, too.

**Key words:** ALT, AST, ALP, Combined exercise, Withdrawal addiction females

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## **Introduction**

Addiction to drugs is one of the most important problems nowadays. The prevalence of using drugs through different parts of society has increased, and the pace of this problem arises in women significantly (1). In most countries, there are no anti-addiction and harm reduction plans related to addicted female's needs, or if there is, it's very rare; so ignoring of this sexuality needs and related factors, had increased vulnerability in women (2). Researchers have different programs in their minds (3). At the moment uses of opioids for controlling and relief of acute pain is more common (4). One of these programs is using methadone in period of quitting drugs (5). The most withdrawal addiction camps use methadone. Methadone is a  $\mu$ -opioid receptor agonist that causes euphoria, analgesia, and other effects of morphine-like drug use. Using the constant amount of methadone does not cause the euphoria of heroin use (6). Methadone has a little solubility in fat, same equivalent potency as morphine; but longer duration of action than it. So, it is slower to penetrate the brain than other drugs; mainly metabolized in the liver, and its plasma half-life is very long and variable (13-100 hours); hence its main use is in the prevention of withdrawal symptoms (7).

Prescription of opioids causes addiction by itself in long time; and leave of consuming this drugs cause some symptoms like fidget, anxiety, violence and irritability that this symptoms so called "Withdrawal syndrome" (7). Also, the addiction may result in high level liver damages (8), so the examining of enzymatic changes could be useful in identifying the source of liver damages. Liver cells contain aminotransferases (transaminases), which are important markers in the diagnosis of liver disease. Any liver damage causes more amounts of them to leak into the bloodstream. Hepatic enzymes of aspartate transaminase, alanine transaminase, and alkaline phosphatase are used to identify such lesions (9). Alkaline phosphatase has known as a tumor marker or indicator of liver and bone diseases. Alkaline phosphatase is a hydrolase enzyme that transfers the phosphate group from a variety of molecules including nucleotides, proteins and alkaloids and its optimal activity is at alkaline pH (8-8.5) (10). This enzyme works sporadically in most body tissues, but the highest amount of enzyme activity is found in the intestines, liver, bone, spleen, placenta and kidney. AST is present in the cytoplasm and mitochondria of cells of the heart, liver and muscle tissues. If these tissues become damaged, serum AST levels increase. ALT, like the AST enzyme, is scattered in most tissues but its amount is much lower than the AST and in acute hepatic lesions, its level raises substantially (11). Even though methadone therapy seems to be the most appropriate method for opioid detoxification today, unfortunately, some withdrawal addicted people by methadone suffer from mental disorders such as anxiety and depression (12). On the other hand, some of these patients do not respond to this treatment. Due to the occurrence of these phenomena, many limitations have been established for clinical uses of these compounds. Accumulated research supports the idea that exercise could be an option of potential prevention and treatment for drug addiction. Exercise has been a potent stimulant of dopamine; hence it seems we can use it to reduce opioid tolerance and dependence. Exercise plays a major role in the health of humans; and increases blood circulation in the liver and accelerate the release of substances through the kidneys. Significant effects of exercise activity with the intensity equivalent to the aerobic threshold on improvement of cardiorespiratory capacity in non-athlete have been reported (13). Aerobic exercise has beneficial adaptation on cardiac autonomic function related to the subject's age, sex, and health or disease states (14). Noori et al (2013) showed that aerobic and strength exercise has reduced inflammatory indicators (such as CRP and fibrinogen) on withdrawal addiction males (15). Exercise holds potential to reduce substance use, but engaging patients in exercise regimens is challenging (16). For example Literature has showed contradictory finding from past research caused by exercise programs to evaluate the activity of triad mentioned liver enzymes in withdrawal addiction people. Also sex-specific exercise intervention strategies may be important for preventing and treating drug addiction in men and women. For example, Haddadi et al. (2012) reported constant values of liver enzymes AST, ALT and ALP in withdrawal addiction females by methadone, subsequent of 8-weeks endurance training (6). Also Sadeghi et al. (2017); reported non-significant effects by 12-weeks of endurance training on ALT and AST liver enzymes in Iranian obese women (17). On the other hand, Davoodi et al. (2012) reported the significant reduction in enzymes of AST and ALT in fatty liver patients on the subsequent of 8-weeks of endurance training (18).

Therefore, due to the harmful effects of drug withdrawal (withdrawal syndrome) as mentioned above, on the one hand, according to vacancy of prior researches about investigating of combined exercise with methadone on the liver enzymes levels of AST, ALT, and ALP, on the other hand, in this study, the efficacy of 8-weeks combined exercise with methadone on liver enzymes has investigated and analyzed.

### Material and Methods

The present study was a semi-experimental. The statistical population of this study consisted of all women between 20-40 years old from Zahedan drugs addiction camp. Inclusion criteria age, duration of drug use, duration of drug withdrawal, type of drug used and body mass index. The exclusion criteria history of heart disease and hypertension, diabetes, kidney and liver disease affecting the levels of liver enzymes, confirmed by a physician. The subjects, were 43 women who took part in the survey, voluntary, and were divided into the methadone (n=20) and methadone with combined exercise (n=23) groups, randomly. All samples were monitored for three months in camp; nutrition was also the same for all and combined exercise protocol according to the Table 1 was applied for "methadone with the combined exercise" groups (15).

**Table 1. Aerobic & Strength Training Protocol\***

Weeks (N)	Days (N)	Warm up (Min)	Aerobic Training		Strength Training			Cool down (Min)	
			Time (Min)	Average distance (Meter)	Maximum heart rate (%)	1RM (%)	Set (N)		Repeat (N)
1 & 2	3	10	15	400-700	40-50	30	3	8	10
3 & 4	3	10	20	700-1000	50-55	35	3	10	10
5 & 6	3	10	25	1000-1300	55-60	40-45	3	12	15
7 & 8	3	10	30	1300-2000	60-70	45-50	3	15	20

\*The protocol was run for eight weeks.

The written and oral information of the study gave to the subjects; informed consent was obtained from all human adult participants. All medical research must be done considering the Helsinki Declaration of 1975, as revised in 2013. The governorship of Sistan and Baluchestan, issued a license to conduct this survey, officially. For the administration of the protocol, a specialist physician, for methadone prescribes, and two exercise physiologists, for combined exercise prescribe were employed.

The protocol of combined exercise and blood sampling, taught to the subjects in one session. In order to reduce the effects of some foods on the inflammatory markers, the participants were asked to refrain from eating fast foods and caffeinated beverages for 24 hours prior to blood sampling (19). It should be noted that the supplement was solubilized daily with 3 cc of water to give the "methadone" and "methadone with combined exercise" groups (20). This amount of methadone remained the same throughout the study and remained unchanged. The training program that had given to the subjects was a combination of aerobic and strength training that performed for eight weeks and three sessions per week. During all sessions the intensity of aerobic exercise controlled by using the "Pular" pulse meter depending on each subjects' heart rate, between 40-70 depend on its associate phase that calculated by Caronen method and checked via finger pacemaker) (15). Strength exercise was performed after aerobic exercise. Surely not everyone attended everything, but exercise physiologists waited and helped them to complete the protocols. The program of strength training was: 2 sets, with 10 repetitions by 30% of 1RM that increased up to 3 sets, with 6 repetitions by 50% of 1RM at the end of the training period. Two minutes rest was considered between all sets. The movements were including of "Chest press, Biceps workout, Dumbbell Row, Abdominal workout and squat". It is noted that the methadone group did not exercise during this

time and just did their physical activities. Groups were just methadone vs. methadone plus exercise. Comparing exercise group alone is not really an ethical design as methadone is a well established intervention with decades of support. To assign someone to a condition without methadone raises serious ethical concerns. The digital height meter to measure the height by 0.01 meter accuracy, and the Germany-made SECA standard medical scale to measure weight by 0.01 kg accuracy was used. Subjects' body mass index was calculated by dividing their weight (kg) by their square height (m<sup>2</sup>), too (21).

**Measuring the enzymes (AST, ALT and ALP):**

Blood samples (5cc each person), pre and post 8-weeks exercise were directly collected from anterior veins of samples in morning at 8 o'clock, at sitting and comfortable position for the assessment of liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP).

Then after blood clot formation, tubes were centrifuged rapidly for 10 minutes at 14000 rpm. To measure the activity of all three enzymes calorimetric and spectrophotometry methods were used via "Pars Lab Company kit"(Tehran, Iran), and the activity of these enzymes was measured via using the instructions of commercial enzymatic assay kits (Cod: 119600R910, 118600R910, and 102600R910, respectively) (22).

The reference range for ALP level was set at 64- 300 (for women) international units per liter and the reference range for AST and ALT was set at 10- 40 (for both men and women) international units per liter (23).

**Statistical analyses methods:**

Data were analyzed descriptively and inferentially using the SPSS-24 Software; the descriptive statistics were used to evaluate the mean and standard deviation of the research variables-related data. Kolmogorov-Smirnov's Explore test was used to check the data distribution were normal. Data were normal, so and base on the used statistic methods in previous literature (21), to compares the means between two groups on the same continuous, independent t-test and to compare two means were from same group (pre test vs. post test) paired t-test were used. The statistical significant level P was taken to be less than 0.05 (P<0.05).

**Results**

The demographic information includes of age, height, body mass, duration of drug use, duration of withdrawal, and body mass index are presented in Table2. Descriptive analyze showed that both methadone & methadone with combined exercise, were not significantly different (p > 0.05). Also, The results of independent t-test showed no significant difference between both groups of methadone & methadone with combined exercise on the AST, ALT, ALP enzyme levels in pre-test, too (P>0.05).

**Table2. Demographic characteristics of the subjects**

Variables	Group	
	Methadone Mean ± Sd	Methadone with Exercise Mean ± Sd
Age (years)	27.4 ± 3.16	29.3 ± 2.3
Weight (kg)	54.27 ± 2.37	52.67 ± 4.32
Height (cm)	157.34 ± 3.25	155.53 ± 3.21
Duration of opiate use	5.1 ± 2.4	5.5 ± 3.7

<b>Duration of opiate withdrawal</b>	1.4 ± 0.7	1.5 ± 0.6
<b>BMI</b>	20.3 ± 5.61	20.7 ± 4.89

Following, the results of data comparing liver enzymes in groups (methadone & methadone with combined exercise) are shown in Table 3. The results of Table 3 showed a significant decrease in liver enzyme levels in most enzyme levels of experimental groups ( $P < 0.05$ ). Just the amount of enzyme levels of ALP in methadone with combined exercise decreased no significantly ( $P > 0.05$ ).

**Table3. Paired t-test to investigate pre and post-test differences in same groups on liver enzymes levels**

Groups	Variable	Pre-Test	Post Test	Paired T Test	P Value
		Mean ± Sd	Mean ± Sd		
Methadone	AST	20.58 ± 5.265	16.75 ± 7.086	-2.349	0.039
	ALT	17.17 ± 7.171	10.08 ± 6.037	-3.195	0.009
	ALP	288.50 ± 65.433	243.50 ± 70.63	-4.453	0.001
Methadone with Exercise	AST	22.00 ± 8.279	13.67 ± 2.570	-3.612	0.004
	ALT	19.00 ± 1.415	9.83 ± 4.407	-2.145	0.005
	ALP	276.58 ± 89.261	254.00 ± 89.889	-1.701	0.117

Table 4 examined the significant statistical difference between the effects of the both methods of methadone & methadone with combined exercise on the AST, ALT, ALP enzyme levels index. The results of independent t-test showed no significant difference between them ( $P > 0.05$ ).

**Table 4. Independent t-test for comparison post-test differences in two groups on liver enzymes levels.**

Enzymes	Group	Post Test	Independent t-test	P Value
		Mean ± Sd		
AST	Methadone	16.75 ± 7.086	1.417	0.170
	Methadone with Exercise	13.67 ± 2.570		
ALT	Methadone	10.08 ± 6.037	0.116	0.90
	Methadone with Exercise	9.83 ± 4.407		
ALP	Methadone	243.50 ± 70.63	_ 0.318	0.75
	Methadone with Exercise	254.00 ± 89.889		

\* Significant level was considered  $P < 0.05$ .

## Discussion

The results showed that both of methods include of methadone & methadone with combined exercise decreased the levels of AST and ALT enzymes, significantly.

These results were agree with the research of Barzegarzadeh and Dabidy (2012) on the title of effect of four weeks of non-exercise following 12 weeks of aerobic training on liver enzyme changes in postmenopausal rats at continuous and interval groups (24); and the research of Davoodi et al. (2012) on the title of effect of Eight Weeks of selected aerobic exercise on fatty liver enzyme Levels (AST, ALT) in Training and Control Groups, that their results showed a significant decrease in enzyme levels (18).

From the other hand the results of the review were different with the findings of Zarandi et al (2012) on the title of study of changes in some liver enzymes and blood lipid levels following regular interval and continues aerobic exercise in older rats that reported significant increase in liver enzymes levels compared to pre-test (24); and the study of Haddadi et al. (2012) on the title of effect of eight weeks endurance training on liver enzymes AST, ALT and ALP of methadone withdrawing female addicts who reported no change in enzyme values (8), and Sadeghi et al. (2017), who reported 12 weeks of endurance training on the levels of ALT and AST liver enzymes in Iranian obese women without significant effect (17).

The results also showed that methadone with exercise group hadn't significant decrease in ALP levels. Mirdar et al. (2008) investigating the effect of an exhaustive exercise session for one week on some liver enzymes in female students and Eriksson et al. (2002) investigating the effect of an 8-Week jumping training on ALP Levels reported a significant increase in ALP enzyme level (25, 26).

Probably the reason for the inconsistency of the results of the present study with the study of Miradar et al. (2008) is the difference in the length and number of training sessions and the periodic time of blood sampling from the subjects (25). Also, the type of supplement used, environmental conditions, status of the subjects, type of exercise protocol, time and method of blood sampling of other studies may be reasons for inconsistency results with other studies mentioned above.

On the other hand, this finding was in line with the results of the researches by Bijeh et al (2011) who had studied the effect of aerobic exercise on bone metabolism markers in middle-aged women following three different jumping protocols (27). Also Rostami et al (2020) reported the decrease of serum levels of ALP after two weeks in training groups compared to sham and alcohol groups (28).

Physical activity causes the ALP to have an anabolic effect on bone metabolism. There are generally two mechanisms for liver damage. One of them is liver injury and the other one is bile duct injury that ALP is used to injure bile ducts in the liver; therefore, this study suggests that exercise and methadone may not have had any effect on bile ducts, likely. Despite much research in this field, the exact mechanism of tolerance, dependence, and opioid use syndrome has not been fully understood; but according to some studies of the mechanisms involved in the phenomenon of tolerance and dependence on opioid compounds, neurotransmitter systems such as Nitric Oxide, (29), Glutamate (30), dopamine (31), and excitatory amino acid receptors, especially the NMDA receptor (32) are important sites.

The results showed no significant difference between the post test level enzymes of AST, ALT and ALP in both methods of methadone & methadone with combined exercise. With activation of the NMDA receptor, calcium entry into the cell increases. Increasing intracellular calcium concentration can obviously activate the type of calcium-dependent secondary prophets and lead to the adverse effects such as the activity of calcium calmodulin II kinase Protein (CaMkII) (33), activity of C kinase Protein (PKC), activates nitric oxide synthetase (NOS) and eventually nitric oxide production (NO) (34). NO is also a nerve modulator derived from L-arginine by the NOS enzyme. Researchers have shown a bilateral relationship between NO production and dopamine release (35). Excitatory calcium-stimulating signals, such as chronic low-frequency neural motor stimulation, exercise (mechanical overload), or voluntary wheel drive - induce a sustained low amplitude increase in intracellular calcium levels, and in turn, the CaN signaling pathway. It also stimulates calcium protein kinase calmodulin (CaMK). CaMK activity, such as CaN, is regulated by intracellular calcium, although the amount and type of calcium message varies. While CaN is activated by tolerating low-amplitude calcium messages, CaMK is likely activated by short- and long-range messages (36).



Some scientists have found that CaMkII can phosphorylate the NMDA receptor, which increases NMDA receptor activity and calcium permeability through the channels. This positive feedback loop between CaMkII and NMDA receptor could be suggested as a mechanism enhancing CaMkII activity and NMDA receptor in opioid tolerance and dependence (37). This could lead to a decrease in dependence on exercise, which could be further explored, especially in team sports for addicts at the time of quitting.

On the other hand, exercise results in the production of glial cell-derived neurotrophic factor (GDNF) from brain stem glial cells. Dopaminergic neurons are also present in the brainstem. Physical activity increases GDNF production; it can lead to survival and growth of dopaminergic neurons (38). GDNF has a protective role against dopaminergic cells, prevents dopaminergic neurons from being vulnerable and increases dopamine release. Michael et al. (2009) showed that GDNF prevents dopamine levels from decreasing (39). Increased blood flow to the brain also plays an important functional role in the survival and maintenance of dopaminergic neurons and adequate oxygen supply to these cells (38). Exercise is a potent stimulant of dopamine and may therefore be used to reduce opioid tolerance and dependence.

### Conclusion

Considering the benefits of exercise such as happiness, confidence, and etc. The method of combined exercise with consuming methadone is an appropriate procedure for withdrawal.

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### چکیده فارسی

تاثیر هشت هفته تمرین ترکیبی توأم با متادون بر آنزیم های کبدی معتادین زن در حال ترک

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با توجه به افزایش میزان اعتیاد در بین زنان و اهمیت نقش فرزندپروری و مدیریت زنان در منزل، اهمیت سلامتی و تندرستی در این قشر از جامعه دوچندان احساس می شود. یکی از عوامل تأثیرگذار بر روی سلامتی، انجام ورزش منظم و مداوم است؛ به همین دلیل هدف از انجام پژوهش حاضر بررسی میزان اثربخشی هشت هفته تمرین ترکیبی توأم با مصرف متادون بر آنزیم های کبدی (ALP، AST، ALT) معتادین زن در حال ترک بود. در این پژوهش نیمه تجربی که در کمپ محبت زاهدان انجام گرفت، ۴۳ نفر از معتادین زن در حال ترک به روش هدفمند و در دسترس به عنوان نمونه پژوهش انتخاب و بصورت تصادفی در دو گروه متادون (۲۰ نفر) و متادون و ورزش (۲۳ نفر) با فاکتورهای مشابه همچون سن، نوع و دوره ترک دارو و شاخص توده بدنی دسته بندی شدند. سطح آنزیم های کبدی از طریق خونگیری در قبل و بعد از هشت هفته اعمال مداخله تمرینی مورد سنجش و بررسی قرار گرفت. جهت مقایسه میانگین بین گروه ها آزمون T مستقل و جهت مقایسه دو میانگین در هر گروه (پیش آزمون در برابر پس آزمون) از آزمون T زوجی از طریق نرم افزار SPSS نسخه ۲۴ استفاده شد. سطح معناداری آماری نیز در سطح  $P < 0.05$  در نظر گرفته شد. نتایج نشان داد سطوح آنزیم های کبدی (ALP، AST، ALT) در هر دو گروه کاهش یافت؛ که بجز ALP در گروه متادون و تمرین ترکیبی ( $T = -1.701, P = 0.117$ ) همگی معنادار بودند ( $P < 0.05$ ). همچنین نتایج آزمون T مستقل تفاوت معناداری را در میانگین مقادیر پس آزمون در آنزیم های ALP، AST، ALT در بین دو گروه نشان نداد ( $P > 0.05$ ). این یک مطالعه موردی خوب بود که بر اساس آن ممکنست یک مطالعه قوی تر با حجم نمونه بزرگتر برای کشف بیشتر یافته های مختلف استفاده گردد و از جنبه های جدید فناوری نشان می دهد که احتمالاً تمرین ترکیبی (هوایی + قدرتی) نیز می تواند یک روش مفید جدید برای بکارگیری همراه با مصرف متادون در زنان معتاد در حال ترک باشد.

واژه های کلیدی: ALP، AST، ALT، تمرین ترکیبی، زنان معتاد در حال ترک.