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The Effect of 8 Weeks of Combined Training with Consuming Methadone on Plasma Fibrinogen & CRP on withdrawal Addiction Women

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Abstract

Background: In addiction field, there is more attention on men than women, while women are more vulnerable to addiction. Because of the importance of women in the family foundation, we decided to investigate this subject. **Purpose:** This study aims at the effect of 8-weeks of combined training with methadone on cardiovascular inflammatory markers fibrinogen and CRP on addicted women. **Method:** This study accomplished as a semi-experimental research. 24 addicted women were randomly selected as samples from Zahedan Mohabbat addiction Camp that divided in two groups of methadone (N= 11) and methadone/ exercise (N= 13) by the same variables such as age, BMI, type and duration of drug withdrawal. The protocol of combined exercise was included of aerobic added to strength training; also methadone was taken according to the camp instructions, too. Blood sampling, pre and post 8 weeks exercise were directly collected from anterior veins of samples and the levels of plasma fibrinogen and CRP were measured in lab. To compares of the pre and post tests means for each group as well as both groups, paired and independent t-test via SPSS software version 24 were used, respectively. Statistical significant level was considered $P<0.05$. **Results:** The results showed that CRP values in both groups decreased significantly (methadone: $P<0.05$, $T=-2.21$ and methadone/ exercise $P<0.05$, $T=-2.63$). Also, plasma fibrinogen values in both groups increased significantly (methadone: $P<0.05$, $T=5.03$ and methadone/ exercise: $P<0.05$, $T=4.21$). Also, there were no significant difference between post-test's levels of CRP and fibrinogen between methods ($P>0.05$). **Conclusions:** It has suggested that the method of methadone/ exercise might be used as such as methadone method by the same results on plasma fibrinogen levels and CRP for withdrawal addiction women.

Keywords: Combined training, Methadone, Fibrinogen and CRP, Withdrawal addiction

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INTRODUCTION

Drug addiction is a special occurrence in today's world, although drug using has been widespread in the past too but it was not considered a social diversion. By spreading of modern culture, modern values and norms increased (Arazih & Asgari, 2012). The history of opium use in Iran has been for at least three centuries and it is reported that among various opioids, opium has the highest consumption among Iranian addicted (Karbakhsh & Zandi, 2007). And unfortunately, our women, who are the main pillar of the family, have also suffered from this crisis. In most countries of the world, addiction treatment and harm reduction programs are either lacking or very rare to fit the needs of addicted women. Therefore, neglecting the needs and gender-related factors leads to increased vulnerability of addicted women (Kazemi et al, 2013). They suggest many treatment options, and one of them is use of methadone-like opioids because of pain and inflammation syndrome (Abidizadegan et al, 2009).

Methadone is a μ-opioid and agonist of the μ-receptor which after consumption, can lead to euphoria, analgesia and other effects of morphine-like substances. Consuming a certain amount of methadone does not cause severe euphoria from heroin use (Abidizadegan et al, 2009). The most effects of drug abuse are on the central nervous system, the auto nervous system and the intestines. However, drug abuse affects other body systems, including the cardiovascular system (Nouri et al, 2013).

Repeated use of opium increases the risk of heart attacks and strokes (Espinola-Klein et al, 2007). For a long time, the fat profile was an indicator of cardiovascular diseases, but the American Heart Association in 1998 proposed measuring inflammatory markers for cardiovascular disease plasma fibrinogen and C-reactive protein (CRP) (Yarnell et al, 2005). Fibrinogen is a high-molecular-weight protein made in the liver with an average level of 250 mg/dl and it increase liver and inflammatory diseases. Increased plasma fibrinogen may be a precursor to increased blood clotting (Yarnell et al, 2005). Fibrinogen, by affecting plasma viscosity, platelet aggregation and the amount of fibrin it forms, provides the basis for coronary artery disease (Nouri et al, 2013). Increasing plasma fibrinogen can be seen along other risk factors for coronary artery disease such as smoking, hypertension,

increasing blood lipids, fibrinogen is an independent risk factor for arteriosclerosis (Sato et al, 2000). A report has shown that the rate of clot formation in addicted patients is higher than in normal people (MiladiGorji et al, 2010). C-reactive protein (CRP) is a sensitive and nonspecific index of inflammation that has been widely studied. This protein binds to a wide variety of substances such as microbial polysaccharides and phosphatidylcholine and damages the cell membrane. C-reactive protein (CRP) also increases the activity of phagocytic cells and activates the classic complement path (Piri et al, 2014). C-reactive protein (CRP) has also been recovered from human atherosclerosis lesions (Helgerud et al, 2007). Nowadays scientists identify addiction as chronic disease due to its undesirable effect on body and they believe that exercise can be effective in repairing and fixing damaged organs (Heidarianpour et al, 2014). MiladiGorji et al. (2010) showed that physical activity reduces the rate of morphine dependence in rats and, therefore, may be a substitute for other therapies as a natural reward. Banitalebi et al. (2010) examined the impact of a course of physical activity on cardiovascular risk factors in drug abusers after quitting; the results showed that physical activity had a positive effect on physical composition and physical fitness factors of addicts after quitting and prevented the increase of cardiovascular risk factors. Noori et al (2013) showed that aerobic and strength exercise has reduced inflammatory indicators on withdrawal addiction males. On the other hand, the result of Saadipour et al research (2008) showed that physical activity is a good way to prevent and treat drug-dependent patients. Iftekhar et al. (2007) showed that adults' inflammatory markers were inversely correlated with their level of aerobic fitness

According to mentioned benefits of aerobic and strength exercise and since there was no study about the effect of combined exercise on inflammatory factors such as plasma fibrinogen and CRP in addicted women, the aim of this study was to investigate the effect of 8-week of combined exercise with consuming methadone on plasma fibrinogen and CRP in withdrawal addiction women.

METHOD

Research design

This research was a semi-experimental study. The sample size include of 24 opium and crystal withdrawal addiction females between 20-40 years old residing in Zahedan drug addiction camp who were supervised and nutritionally coordinated for three months in the camp. Samples were divided into two groups of methadone (N= 11) and methadone and exercise (N= 13) and the training program was run for 8-week as mentioned by Noori et al (2013).

Procedure

At the beginning of the program, the procedure was explained to the samples and written consent forms were obtained from them. The Zahedan governorate was officially licensed to conduct this research. Then both groups were compared according to height, weight, age, duration of drug use, duration of drug withdrawal, type of drug used, body mass index, that there was no significant difference between them. Also the present study was conducted under the supervision of a specialist physician to prescribe methadone (according to camp instructions) and an exercise physiologist to perform the exercises correctly (as mentioned by Noori et al, 2013) during 8-week of exercise. Base on the medical approval, they had no experience of heart disease and hypertension, diabetes, kidney and liver disease affecting fibrinogen levels. Then the subjects were introduced about the blood sampling in one session. In order to reduce the effects of food on the inflammatory markers, the participants were asked to refrain from eating fast foods and caffeinated beverages for 24 hours prior to blood sampling. Blood samples were taken 24 hours before and after 8-week exercise program while they were fasting about 8-10 hours. Serum ELISA kit (British Randox) was used to determine high sensitivity CRP. The minimum process sensitivity of the processor and kit was 0.01 mg / dl and the coefficient of variation between and within the process was 1.5 and 2.5%, respectively. Plasma fibrinogen levels were measured by coagulometry using a Quatroncoagulometer. Glasasu clotting technique was used to determine the plasma fibrinogen content of 10 TEC lot.Water-soluble supplements were also given 3cc daily to

the methadone and methadone-exercise groups. The amount of methadone was constant throughout the plan and didn't change.

The training program given to the subjects was an aerobic/ strength program that lasted 8-week and three sessions per week (Noori et al, 2013). The researchers monitored the intensity of exercise depending on the subjects' heart rate before and after exercise, during and after each session, using a Pulsar pacemaker (Table 1). The strength training program was also performed for 8-week and three sessions per week after aerobic training. Resistive exercises consisted of two sets of 10 repetitions by the intensity of 30% of one repetition maximal (1RM). At the end of the training period, three sets of 6 repetitions by the intensity of 45-50% of 1RM were performed with two-minute rests to observe the progressive overload principle.

In the second, fourth, and sixth weeks of the exercise, one repetition maximum of movements was measured again, which included chest press, bicep curl, dumbbell row, sit-up and squat. It is noteworthy that the methadone groups did no physical activity during this time, and only did the same routine tasks as previous. Subjects' height was measured with a 0.01 meter accuracy meter and their weight was measured with a digital weighing accuracy of 0.01 kg and body mass index (BMI) was calculated from the fraction of weight to squared height. Also, the heart rate of subjects was measured by pulse meter.

Data Analyses

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. We use shapiro-wilk for normality test. Since data were normal, 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 meaningfulness level P was taken to be less than 0.05 ($P < 0.05$); and to draw charts and prepare tables, use was made of the descriptive statistics methods and the Excel (2010) program.

RESULTS

Initial data obtained from the subjects including age, weight, height, duration of drug use, duration of drug withdrawal and BMI are summarized in Tables 1 & 2, respectively.

Table 1: Demographic characteristics of the subjects

Variables	Methadone group AVG ± Standard deviation	Meth-Exer group AVG ± Standard deviation
Age	25.45±3.19	27.64±2.34
Weight (kg)	54.27±2.37	52.67±4.31
Height (cm)	157.34±3.25	156.53±3.21
Duration of drug use (year)	5.1±2.4	5.5±3.7
Duration of quitting (months)	1.4±0.7	1.5±0.6
BMI (kg/m2)	20.3±5.61	20.7±4.89

*AVG: Average

Table 2: Aerobic-Strength Training Protocol

Weeks (N)	Session (N)	Warm-up (Min)	Aerobic Exercise			Strength Exercise			Cool down (Min)
			Time	Average Distance (Meter)	Maximum Heart rate (%)	%1RM	Set	Repeat	
1st & 2nd Weeks (Compatibility)	3	10	15	400-700	40-50	30	3	8	10
3rd & 4th Weeks	3	10	20	700-1000	50-55	35	3	10	10
5th & 6th Weeks	3	10	25	1000-1300	55-60	40-45	3	12	15
7th & 8th Weeks	3	10	30	1300-2000	60-70	45-50	3	15	20

The results of paired t-test showed that CRP post tests values in both methadone and methadone-exercise groups decreased significantly ($T = -2.21$, $P < 0.05$, and $T = -2.63$, $P < 0.05$, respectively). Independent t-test results showed that the CRP values of post test between groups

were not significantly different (P > 0.05, T =-1.14). Also, the results of paired t-test showed that plasma fibrinogen post tests values in both methadone and methadone-exercise groups increased significantly (T = 5.03, P <0.05, and T = 4.21, P <0.05, respectively). Independent t-test results showed that the plasma fibrinogen values of post test between groups were not significantly different (P > 0.05, T = 1.39) (Table 3).

Table 3: Comparison of CRP & fibrinogen values in all groups

Variables	Groups	Pre-test values	Post-test values	paired t-test	P	Independent t-test	P
CRP	**Methadone**	23.37±4.06	19.37±5.16	-2.21	*0.031	-1/14	0.90
	Meth-Exer	23.61±3.89	20.67±4.76	-2.63	*0.034		
Plasma fibrinogen	**Methadone**	166.4±11.33	229.11±12.67	5.03	*0.023	1.39	0.07
	Meth-Exer	168.2±13.17	197.63±12.27	4.21	*0.006		

(*Significance level P <0.05)

DISCUSSION

There has been no research on the effects of exercise and methadone on plasma fibrinogen and CRP. This makes it difficult to compare the present study with those of other studies. In this study, plasma fibrinogen levels of addicted women after 8-week of exercise and methadone consumption were increased, significantly.

The results are consistent with those of Banitalebi et al. (2010), MiladiGorji et al (2010) and Maesomi et al. (2001), but differ from those of Nouri et al (2013), Ernst (2003), Foody and Pearce (2002) that show the decreasing in fibrinogen, and LeMura and Duvillard (2004) and Monica (1997) that show that there is no significant relationship between exercise activity and plasma fibrinogen. This lack of relevance may be related to the type of subjects because the subjects of the Nouri et al (2013) study were male and the subjects of LeMura and Duvillard (2004) and Monica (1997) were heart patients. Maesomi et al. (2001) showed that plasma fibrinogen levels were significantly higher in opium addicted men than in non-opium users. Although the mechanism of fibrinogen elevation in addicts is unclear, this issue is of great importance because plasma fibrinogen is an independent risk factor for coronary artery disease (Maesomi et al, 2001). The results showed that the rate of clot formation in opium addict patients is higher than non

addicts (Sato et al, 2000). The results of this study show that regular exercise with methadone as well as methadone consumption, can be effective in increasing the true plasma fibrinogen level in addicted women. It may be argued that this increase is a form of adaptation to exercise that directly or indirectly increases the production of fibrinogen. Also increased VO_2 max and fitness are all reasons for effectiveness exercise and adaptation to increasing fibrinogen values. Factors affecting blood rheology include blood viscosity, plasma viscosity, hematocrit, and plasma proteins such as fibrinogen. Blood viscosity is the most important determinant of blood rheology (Nazarali et al., 2013). Most researchers, such as Brun et al. (2004), after exercise, have observed an increase in blood viscosity, one of the most important factors affecting blood rheology. Previous reports have suggested that exercise protocols of varying intensity and duration typically result in increased plasma viscosity and hematocrit often resulting from a decrease in fluid, known as increased blood concentration. Also, hemorrhagic changes due to exercise can be caused by the release of new proteins into the bloodstream (Brun et al, 2007). In some studies, the lack of increased erythrocyte accumulation after exercise has been attributed to an increase in blood proteins, especially fibrinogen, and often a decrease in its accumulation is attributed to increased concentrations of lecithin and albumin (Omori et al, 2010). Since fibrinogen is one of the major determinants of plasma viscosity, regular exercise results in increased plasma volume, increasing blood rheology, and decreasing blood viscosity reduces plasma fibrinogen.

In the present study, CRP levels decreased significantly after 8-week of combined exercise consuming methadone in both methadone and methadone/ exercise groups, which is consistent with the findings of Nouri et al. (2013), Maesomi et al. (2001), Asgari et al. (2008) concurred in reducing CRP but did not agree with the results of Torzewski et al. (2000) and Naderi et al. (2007). This inconsistency probably depends on the type of subjects that used the animal samples. Creating of CRP and coming in with antigens stimulates immune complexes, bacteria and fungi. After entering the CRP into the bloodstream and binding to the surface of the microorganisms, activates the complement pathway, which is part of the immune response (Smith

et al, 2015). CRP appears to be the primary defense mechanism against infections and removes toxins from surface of body tissues. Increased serum CRP levels indicate an increase in inflammation, especially arterial atherosclerosis, which confirms the effect of drugs abuse on the immune system and results that addicts are at greater risk of cardiovascular disease than healthy people (Blake & Ridker, 2001). In people with low cardio-respiratory readiness, CRP levels may decrease with increasing physical readiness even without losing weight (Church et al, 2002). The findings show that whatever the aerobic power is higher, the plasma CRP level is lower (Witkowska, 2005). Plasma CRP levels were lower in the addicts who were in the methadone group versus methadone/exercise groups due to their increased aerobic capacity. This result is inconsistent with the results of Nouri et al. (2013). In the study by Nouri et al (2013), subjects were male. The fact that exercise increases plasma CRP levels is consistent with the results of Torzewski et al. (2000) and Naderi et al. (2007), with the explanation that those subjects were not the same as our subjects.

CONCLUSIONS

Levels of inflammatory markers in addicts are high, and in this study the methods of methadone and methadone/ combined exercise had the same affects on CRP and plasma fibrinogen levels. Hence it can be suggested that the protocol of combined exercise with methadone could be use for withdrawal addiction women, too.

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