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THE EFFECT OF A PERIOD OF NON-CONTINUOUS AEROBIC EXERCISE ON FERRITIN, LIVER ENZYMES AND THERAPEUTIC PROCESS OF ADOLESCENTS WITH BETA-THALASSEMIA MAJOR IN THE MAINTENANCE TREATMENT PHASE

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ABSTRACT

The aim of present study was to investigate the effect of a period non-continuous aerobic exercise on the ferritin, liver enzymes and therapeutic process of adolescents with beta-thalassemia major in the maintenance treatment phase. The statistical population included all the adolescents with beta-thalassemia major visiting the hospitals of Tehran for treatment in 2014. Targeted sampling method was performed. Statistical sample comprised 26 adolescents with beta-thalassemia major vising Zafar Adolescent Thalassemia Clinic and three other clinics in 2013-2014 for treatment and were assigned to two equal control (n=13) and exercise[1] (n=13) groups. The independent variable included 8 weeks of non-continuous aerobic exercise with %50-65 heart rate reserve, for 45 minutes per session, three times a week. The dependent variables consisted of Ferritin and elevated liver enzymes of Aspartate Transaminase (AST) and Alanine Transaminase (ALT) and Alkaline Phosphatase (ALP). Blood samples were collected immediately before and 48 hrs after the last training session. All the subjects went to the laboratory between 9 to 11 am for blood sampling. The results of ANCOVA showed a significant decrease in ferritin (P=0.000) and liver enzymes of AST (P=0.015) and ALP (P=0.005). However, there was not any significant difference in the level of ALT enzyme. The paired t-test results did not found any significant difference between the levels of AST, ALT and ALP, respectively (p=0.188), (P=0,924) and (P=0.172) in pretest and posttest while there was a significant difference between the levels of ferritin in pretest and posttest (P=0.000). According to the results, it can be concluded that the 8-week non-continuous aerobic exercise significantly decreases iron reserve and some liver enzymes in patients with beta-thalassemia major so that it can be used as a supplement to the treatment.

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Introduction

Liver is the primary source of iron storage and the only source of transferrin and ferritin synthesis. Released ferrous iron is highly toxic. Unbounded iron catalyzes the free radicals that causes lipid peroxidation and has toxic effects on the liver. Lipid peroxidation can be the initial reaction of the secondary liver cell lesions to iron overload. Evidence have suggested that liver endothelial cells release ferritin in response to elevated oxidative stress and lipid peroxidation. Several in-vitro and in-vivo studies showed that the pro inflammatory cytokines of hepatocytes such as TNF-a, increase transcription of ferritin mRNA in macrophages, transfer it to hepatocytes and subsequently increase serum ferritin levels. One of the disease that leads to iron overload is thalassemia. Thalassemia is the most common genetic disorder in the world (1). Beta thalassemia is the most prevalent type of the disease which appears in three types of minor, Intermedia and major (2). Currently, Iran lies on the world's thalassemia belt having over 3 million patients with thalassemia minor and 25 thousand patients with thalassemia major (3) to the number of which about 1000 patients are added each year (4). So far, more than 150 gene mutation have been identified for thalassemia (5 & 6). In beta thalassemia, β chain gene is disrupted. Thalassemia major and severe anemia occur when both beta genes are impaired. The vicious cycle is repeated due to anemia and EOP[2] rise (7 & 8) and an ineffective erythropoiesis occurs in the bone marrow. The combination of two agents of ineffective erythropoiesis and severe anemia in patients with thalassemia major causes severe enlargement of bone marrow spaces in these patients and ultimately leads to skeletal deformities. Moreover, extra medullary hematopoiesis enlarges the liver and spleen; that's why these patients need blood transfusion since the early ages of life to compensate for anemia (9). Furthermore, long-term blood transfusion leads to iron overload and toxicity and ultimately damages the heart muscle, liver and endocrine glands. Although serum ferritin is an inexpensive and available method to assess iron overload, it shows only %1 of the total iron reserve and its measurement is affected by liver problems and inflammations (10). Liver iron is an appropriate alternative to the total body iron which has been used as a method for monitoring the treatment of iron excretion in recent years (11). Meanwhile, several recent studies have suggested that aerobic exercises decrease ferritin and iron levels. For instance, Vashtani et al. (2009) investigated the effect of an 8-week aerobic rehabilitation program with moderate intensity of %55 VO_2Max[3] on the concentration of serum ferritin, iron, and TIBC[4] of adolescents with thalassemia major; they found that the mean serum ferritin and iron significantly decreased after 8 weeks of aerobic exercises (12). Sadeghian Shahi et al. (2001) investigated the effect of submaximal aerobic exercise on the levels of iron, ferritin and TIBC in patients with thalassemia major; they found that serum ferritin and iron decreased immediately after the exercises while they had a significant increase after 48 hours of aerobic exercises (13). Even though these studies have shown the effect of aerobic exercises on the reduction of serum ferritin and iron, no study has been done yet to investigate the effect of excretion of ferritin and iron overload on the liver enzymes of patients with beta thalassemia major. Therefore, the present study intended to investigate the effect of an 8-week non-continuous aerobic exercise on the liver enzymes.

Materials and Methods

After proposing the present project to Iran Blood Transfusion Organization and receiving the required licenses, about 26 adolescents with thalassemia major were selected from Zafar Adolescent Thalassemia Clinic and Baharlou, Torfeh and Shariat Razavi hospitals and invited to participate in the current study through announcements, telephone conversation or in person once their records and dossiers were reviewed. The mean and SD of the age and weight of the control group were respectively equal to 16.61±1.98 years and 55.38±7.90 kg while they respectively equate to 16.76±2.08 years and 54.61±6.37 kg in the exercise group. The inclusion criteria encompassed LVEF[5]>%55, SPAP[6]<30 mmHg, absence of diabetes, presence of lower extremity fractures, splenomegaly, and intake of hydroxyl urea. The exclusion criteria involved iron overload in the heart and liver, nausea and vomiting during the exercise, heart diseases, LVEF<%55, SPAP>30 mmHg, and personal tendency to be excluded from the study. Once the subjects[7] were selected, they were provided with explanations about the procedure and problems of the exercise as well as the habits affecting the exercise including nutrition, conditions of drug intake, lack of physical activity (in control group), and observing the conditions of blood sampling in a briefing session. Moreover, they were provided with physical activity readiness and consent forms to admit their readiness. Afterwards, the subjects were asked to record their resting heart rate at standard conditions that had already been described to them. Before any exercise intervention, the patients underwent echocardiography tests in Firouzgar Hospital to determine their LVEF and SPAP. The exercise protocol was carried out in the rehabilitation clinic of Tehran heart center along with heart rate monitoring. In the present pilot project, the heart rate increased to a range of %10 higher than the intended hear rate. After two weeks, all the subjects went to the laboratory between 9 to 11 am for blood sampling. Once initial tests were taken, the subject were randomly assigned to two equal control (n=13) and exercise (n=13) groups. According to the exercise protocol i.e. the 8-week non-continuous aerobic

[2]-Erythropoietin
[3]-Maximal Oxygen Consumption
[4]-Total Iron Binding Capacity
[5]-Left Ventricular Injection Fraction
[6]-Systolic Pulmonary Artery Pressure
[7]-Participants

exercise, the subjects did individual or in-pair workouts with 50-55 percent of heart rate reserve for three 10-minute sets with 5-minute break intervals in the first eight weeks. Each session, the exercise intensity increased by 5 percent so that it reached 60-65 percent of heart rate reserve in the session 17 and this intensity was maintained until the end of the eight weeks. Before increasing the exercise intensity, the 10-scaled Borg Rating of Perceive Exertion was used to measure the subjects' perception of exercise intensity level. For relative control of awareness of their nutritional status, a 24-hour dietary recall was recorded and obtained from the subjects. Finally, 48 hours after the last session of the exercise, the subjects went to the laboratory for the second sampling. $SPSS_{21}$ was used for data analysis. Accordingly, Kolmogorov-Smirnov test was used to ensure the normal distribution of samples and Levine's test was used to verify the homogeneity of variances. Moreover, in order to investigate the difference between pretest and posttest in both groups, the paired t-test was used. To determine the difference between both groups, ANCOVA was used. The significance level was considered as P≤0.05.

Table (1): Patient Demographics, Ferritin and Liver's enzymes Indices

Variable	**Mean**	**SD**	**Rang**
Age	18.96	2.94	12.4-23.6
Weight (kg)	54.62	7.10	48.3-78
Height (cm)	164.04	8.57	153-184
BMI (kg/m^2)	20.26	1.91	17.8-31
Year of Transfusion	14.7	6.3	6-21
Year of chelation	17.2	5.1	3.5-22
Programmed distance(m)	2769.24	85.09	1803-3150
)U/L(AST	38.46	20.99	15-91
)U/L(ALT	29.54	23.36	8-116
)U/L(ALP	318.08	215.395	80-803
Ferritin(ng/ml)	1748.50	1079.29	428-5126
Ejection Fraction (%)	55.3	4	50-60
Pulmonary Artery Pressure(mm Hg)	27.3	7.4	18-31
DBP during Passive rest	63.1	11.32	60-74
SBP during Passive rest	126.65	9.4	118.91-133.6
Splenectomy (Yes/No)	6:23		

Table (2): ANCOVA Results

Parameter	DF	F	P
Level of AST (pre-test)	1	16.133	0.001
Group Effect	1	6.873*	0.015
Level of ALT (pre-test)	1	10.63	0.003
Group Effect	1	0.767	0.390
Level of ALP (pre-test)	1	256.50	0.000
Group Effect	1	9.72**	0.005
Level of Ferritin (pre-test)	1	173.55	0.000
Group Effect	1	88.24**	0.000

** Indicates that P≤0.01 level is significant * Indicates that P≤0.05 level is significant

Table (3). Paired t-test Results

Group	Variable	Pre-test M±SD	Post-test M±SD	DF	t	P
Exercise	AST	34.23±20.00	27.15±11.50	12	1.39	0.188
	ALT	28.61±18.20	28.38±15.84	12	0.098	0.924
	ALP	251.61±123.54	227.00±92.92	12	1.454	0.172
	Ferritin	1793.38±819.12	807.76±361.28	12	7.022**	0.000

** Indicates significant difference in P≤0.01 level * Indicates that P≤0.05 level is significant

Results

According to the results of Table (2), there was a significant difference in the liver enzymes of Aspartate Transaminase (AST) and Alkaline Phosphatase (ALP) and ferritin levels of adolescents with thalassemia major between the control and exercise group after eight weeks of non-continuous aerobic exercise. This difference was not observed in Alanine Transaminase (ALT) level. Besides, Table (3) shows that there was a significant difference between only the ferritin levels of the exercise groups in pretest and posttest. However, there was not any significant difference between the liver enzymes of the exercise group in pretest and posttest.

Discussion and Conclusion

The ANCOVA results showed a significant decrease in the liver enzymes of AST (P=0.015) and ALP (P=0.005) while not any significant difference was observed in the ALT level of both groups. According to the results of paired t-test, only serum ferritin of the exercise group had a significant decrease (P=0.000) in the posttest than pretest. Vashtani et al. (2009) investigated the effect of an 8-week aerobic rehabilitation program with moderate intensity of %55 VO_2Max on the concentration of serum ferritin, iron, and TIBC of adolescents with thalassemia major; they found that the mean serum ferritin significantly decreased after 8 weeks of aerobic exercises (12). On the contrary, Mostahfezian (2005) studied 30 students with an 8-week exercise protocol, three 60-minute session a week at %60-90 intensity of maximum heart rate. They found that aerobic exercise did not have any significant effect on iron, serum ferritin and TIBC (14). The justification for the ferritin decrease during aerobic exercises is that the levels of body iron and ferritin reduce as a result of red blood cell hemolysis, increased body temperature, iron excretion via urine or sweeting and gastrointestinal bleeding. Also, failure to replace the missed iron through nutrition makes the body use the iron reserve (ferritin) that, in turn, reduces the ferritin level. On the other hand, some small molecules such as sugars (carbohydrates), adenosine triphosphate and probably amino acids may act as iron excretion agents. Moreover, iron absorption in patients with thalassemia major increases to 7 times higher than normal people due to blood transfusion and physiological conditions in patients. In such conditions, the effect of physical activity is naturally unequal in both groups because high in level in patients with thalassemia major is more accessible and excreted during the exercise. The results of the present study were in line with the findings of Rink et al., Newlin et al. and Vashtani et al. while they were not consistent with the findings of Fouji et al. and Mostahfezian et al. Regarding liver enzymes, the findings of the present study were consistent with the results of Bijeh et al., Barzegarzadeh et al. and Salahshour et al. Bijeh et al. (2012) studied the effect of an 8-week swimming exercise on the liver enzymes and hematological indices of young women. In their study, the experimental (exercise) group practiced exercised for eight weeks, three sessions a week, 60-90 minutes per session with %65-85 intensity of maximum heart rate reserve. They found that AST level decreased in the exercise group while ALT remained unchanged (15). The results of the present study were not in line with the findings of Mendonca et al., Mena et al. and Zarandi et al. Mena et al (1996) studied the changes in plasma enzyme activities in professional racing cyclists. About 66 cyclists participate in three races with different distances (34 cyclists for 800 kg in 6 days; 15 cyclists for 2700 kg in 20 days and 17 cyclists for 234.5 kg). The results showed that the enzymes of AST, ALT and ALP increased after the exercise (16). The probable reasons for this difference include exercise time, muscular damage during the exercise, type of analyzed sample and carbohydrate consumption (sugar intake). Furthermore, Mendonca et al. (2008) studied the liver enzyme of ALP after triathlon competitions that require higher aerobic capacity. They found that long-term and endurance exercises, requiring high aerobic energy respiration, were effective in enzyme activities of ALT and AST because these activities require more energy through aerobic respiration. ALT and AST enzymes are involved in liver metabolism because liver is more engaged in these activities than other activities. Therefore, the likelihood of liver cell membrane damage is higher during long-term and endurance exercises. However, the present study had rest intervals between phases of activities (17). In addition to genetic and environmental factors, researchers have proposed several assumptions including hypoxia, heat stress and hemolysis, cell lesions caused by physical activities via mechanical processes, changes of plasma volume, peroxidation processes caused by oxygen free radicals, and changes in membrane permeability after the activities in order to justify the elevated liver enzymes (18). In-vivo studies showed that endurance exercises prevented the increase of plasma enzymes of AST and ALT in the subjects exposed to pressure by heat shock protein (HSP70) (19). The results of the present study showed that non-continuous aerobic exercises decreased ferritin and increased or maintained liver enzymes; if liver enzymes are considered as biomarkers of liver damage, these type of exercises not only do not damage liver cells but also maintain their health level. Likewise, Soleiman et al. found that there was a positive relationship between the levels of ferritin and ALT in patients with thalassemia major (20). That is, ALT increases as ferritin rises. According to the results of the present study and Soleiman's et al. study, it can be concluded that aerobic exercises reduced serum ferritin or, in other words, prevented the increase of this enzyme in the body, as it is evident in the pretest and posttest of control group while they kept ALT stable and unchanged in the exercise group, this effect was statistically insignificant, though.

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