



2528-9705

Örgütsel Davranış Araştırmaları Dergisi
Journal Of Organizational Behavior Research
Cilt / Vol.: 3, Sayı / Is.: S2, Yıl/Year: 2018, Kod/ID: 81S2155



EFFECT OF DIFFERENT DOSES OF FLAXSEED OIL ALONG WITH AEROBIC EXERCISE ON PRO-INFLAMMATORY FACTORS IN VISTAR MALE RATS

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ABSTRACT

Introduction: Systemic inflammation plays an important role in the development of atherosclerosis. IL1 β and TNF- α are the most important inflammatory markers in the pathogenesis of atherosclerosis that the effect of physical activity and herbal medicine on its response is not well known. Method: Experimental study was performed and 36 adult male Wistar rats were randomly divided into six groups, including control, practice, linen dose of 10 mg / kg, linen dose of 20 mg / kg, flax training dose of 10 mg / kg, kg20 divided. The training groups performed aerobic exercises for rodents at a specific hour during the day for 8 weeks and five weeks each week. Fat oil groups consumed flaxen every day for 8 weeks. After the end of the period, blood samples were taken from rats and used for the measurement of IL1 β and TNF- α . For analysis of data, Kolmogorov Smirnov test, one way analysis of variance and LSD post hoc test were used. All data was analyzed using SPSS17 software ($\alpha \geq 0.05$). Results: IL1 β and TNF- α decreased in all groups compared to control group ($\alpha \geq 0.05$). Conclusion: In general, the results of this study showed that the combination of training and flaxseed oil reduced IL1 β and TNF- α compared to the control group. Therefore, it is likely that this method can be used as a way to prevent cardiovascular disease and other inflammatory diseases.

Keywords: Cardiovascular Diseases, Inflammation, Atherosclerosis, Aerobic Exercise.

INTRODUCTION

One of the most important coronary artery diseases is atherosclerosis, which its pathological alterations begins from childhood ages and appears in higher ages. In the other word, pathogenesis of atherosclerosis progresses as the age goes higher, and eventually results to disability and mortality in old ages (Blake, Ridker, 2002). Studies indicated that inflammatory factors play important roles in development and progression of atherosclerosis (Kargarfard et al., 2016). Actually, increase in the levels of pro-inflammatory parameters result to adhesion of leukocytes to vascular endothelium, and eventually, atherosclerosis. Decreasing inflammation is a strategy for decreasing cardiovascular diseases, and scientists are working to reduce inflammatory diseases, including cardiovascular disease, by reducing inflammation (Kargarfard et al., 2016). So, some plasma inflammatory parameters are indicated to predict the risk of Coronary artery problems. In this case, TNF- α and IL1 β pro-inflammatory cytokines that can increase and stimulate vascular endothelial activities, are introduced as new inflammatory parameters, and have high sensitivity and specificity in prediction of cardiovascular disease.

They also play an important role in atherosclerosis pathogenesis (Blake, Ridker, 2002; Blake, Ridker 2001; Geffken et al., 2001). High levels of inflammatory parameters in serum are important risk factors for development of cardiovascular diseases (Rohde et al., 1999; Signorelli et al., 2003; Tousoulis et al., 2003). Widely showed that physical activity can reduce inflammation, and consequently prevent cardiovascular diseases. Recent studies also indicated that weight reduce via nutrition intervention and physical activity is effective on prevention and treatment of cardiovascular diseases (Kargarfard et al., 2016; Signorelli et al., 2008; Tousoulis et al., 2003). It is also shown that physical activity is a factor that can decrease inflammatory parameters; so, it could be used for atherosclerosis reduction (Tousoulis et al., 2003; Goldhammer et al., 2005). Moreover, other studies showed the effect of physical exercises on TNF- α and IL1 β pro-inflammatory cytokines, as vascular endothelial activators (Signorelli et al., 2003; Tousoulis et al., 2003; Goldhammer et al., 2005; Nemet et al., 2002; Ziccardi et al., 2002). A study indicated that a period of endurance physical activity in the patients affected by heart disability could significantly reduce TNF- α (Adamopoulos et al., 2001). Another study assessed the effect of 12 weeks of exercise on activity of inflammatory parameters. The exercise program included 45 minutes of aerobic exercise with 70-80% H_{rmax}, for 12 weeks. The results indicated that aerobic physical activity can significantly reduce TNF- α , IL1 β , IL-6, and CRP; however, the level of IL-10 which is a cytokine inhibitory agent, significantly increased (Goldhammer et al., 2005). While it is reported in another study that aerobic exercises for 10 weeks results to increased insulin sensitivity in fat and overweight girls, no significant difference is showed in body weight and body fat percent, as well as levels of pro-inflammatory factors such as TNF- α , and CRP (Nassis et al., 2005). A study indicated that running on treadmill for 30 minutes per day, and for 1-3 weeks can significantly reduce sICAM-1 and pro-inflammatory cytokines levels (Ding et al., 2004; Wang et al., 2001). Moreover, the study performed on male Vistar rats indicated that aerobic exercise for 3 weeks (3 session per week), can significantly reduce levels of sICAM-1 and pro-inflammatory cytokines such as TNF- α and IL1 β (Mogharnasi et al., 2009). In another study, it was shown that an intense aerobic interval training course (HIIT), and aerobic and continuous exercise, can reduce levels of vascular inflammation parameters, and eventually is effective on prevention of cardiovascular diseases (Kargarfard et al., 2016). On the other side, some of nutrient agents that have anti inflammation effect, may be effective in the process of cardiovascular diseases (Aviram, 1996). Flaxseed seeds consisted of omega 3 and omega 6 fatty acids, and studies indicated that flaxseed seed oil have several biological functions such as anti-inflammatory and antioxidant effects (Dimitrijevic et al., 2018; Han et al., 2017; Hashemzadeh et al., 2017). Results of some studies showed that omega 3 and omega 6 fatty acids, which can be found in flaxseed seed oil, is effective in prevention of cardiovascular and inflammatory diseases (Zuk et al., 2011). Besides, recently, anti-inflammatory effects of omega 3 fatty acids attracted many attentions (Sneddon et al., 2008). Several evidences achieved of last studies indicating that omega 3 fatty acids is effective in prevention and treatment of cardiovascular diseases (Connor & Connor, 1997). Several studies attributed Omega-3 to anti-inflammatory effects of flaxseed oil (Zhu et al., 2018). Recent studies also indicated that usage of flaxseed seeds can reduce cholesterol and increase immune system health (Deng et al., 2011; Chytilova et al., 2013; Chytilova et al., 2014; Green, 1986; Tanna et al., 2012; Tuluze et al., 2012; Williams et al., 2007). Other studies showed that flaxseed oil could reduce oxidative stress and factors related to inflammation development in dialysis patients. The



positive effects of flaxseed oil on lipid profile, plasma glucose, and weight reduce are also showed (Akrami et al., 2018; Nounou et al., 2012). Just one study in 2012 has assessed simultaneous effect of physical exercise and flaxseed oil, which indicated that this simultaneous effect can significantly decrease levels of TNF- α and IL1 β in ischemic rats (Nounou et al., 2012). On the other hand, studies showed that intensity, duration, and type of physical activity, are factors that can deeply effect on inflammation process. Until now, simultaneous effect of aerobic exercise and usage of different doses of flaxseed oil on TNF- α and IL1 β , vascular inflammatory factors, has not been studied. Regarding this, the aim of this study is to determine simultaneous effect of aerobic exercise and usage of different doses of flaxseed oil on TNF- α and IL1 β . The present study is designed and performed to find the effect of this combination.

METHOD

In this study, 36 male Vistar rats selected as statistical population. For performing the research, rats randomly divided to 6 groups: Control group, exercise group, 10 mg/kg flaxseed group, 20 mg/kg flaxseed group, 10 mg/kg flaxseed along with exercise group, and 20 mg/kg flaxseed along with exercise group. For each 100 gr of rat weight, 10 gr food placed in the cage every week. For nutrition of complementary groups, after preparation of flaxseed seed and cleaning it, flaxseed oil extracted using specific lubrication machine. Afterwards, based on rat weight, two doses administered to complementary groups using gavage.

Exercise group performed specific exercises, which was included running on the rodent treadmill at determined hours of the day, for 8 weeks (5 sessions per week). First, rats gotten familiarized to the function on rodent treadmill to reduce stress of new environment in them. Familiarizing program included 5 sessions of running on treadmill with 5 to 10 meter per minute, for 10 minutes per day. Activity intensity in first two weeks begun from 10 meter per minute, for 15 minutes; the intensity and duration of this activity increased once per two weeks, in the way that in the last two weeks, the intensity of aerobic activity reached to 22 meters per minute, for 30 minutes. Treadmill slop kept on 5 degree during exercise term. In each session, 5 minutes of warming and 5 minutes of cooling considered which performed by running 5 to 10 meters per minute (Lippincott & Wilkins, 2013). Exercise protocol continued to 72 hours before scarifying the rats.

After collecting blood sample, for plasma extraction, samples centrifuged for 15 minutes in 3000 rotation per minute. For biochemical analysis and assessing the values of TNF- α and IL1 β , ELISA commercial kits of Koma, and ELISA reader instrument were used.

All data reported based on mean and standard deviation. The Shapiro-Wilk test is used to diagnose the normal distribution of data. For assessing differences between and within groups, one-way ANOVA and LSD follow up tests in the significance level ($\alpha \leq 0.05$) were used (using SPSS 17 software).

RESULTS

Analysis of data indicated that both TNF- α , and IL1 β , were decreased due to exercise and complementary flaxseed seed. After aerobic exercise along with using flaxseed seed oil for 8 weeks, mean of IL1 β decreased in all groups in comparison to control group. The same finding



also achieved in TNF- α . Data assessment showed that the simultaneous effect of exercise and usage of flaxseed oil resulted in higher decrease in both variables (TNF- α , and IL1 β). However, highest reduce showed in the exercise along with complementary flaxseed oil dose (Table 1).

Table 1: changes in mean and standard deviation of studied variables

Variables	Groups	Number	Mean \pm SD
IL1 β	Control	6	70/155 \pm 16/2201
	10 mg/kg flaxseed	6	72/171 \pm 16/2124
	20 mg/kg flaxseed	6	55/199 \pm 5/2016
	Exercise	6	12/200 \pm 1970
	10 mg/kg flaxseed along with exercise	6	35/126 \pm 66/1881
	20 mg/kg flaxseed along with exercise	6	98/156 \pm 83/1783
TNF- α	Control	6	66/37 \pm 4/1286
	10 mg/kg flaxseed	6	72/41 \pm 16/1252
	20 mg/kg flaxseed	6	75/49 \pm 16/1233
	Exercise	6	51/42 \pm 16/1233
	10 mg/kg flaxseed along with exercise	6	97/18 \pm 16/1191
	20 mg/kg flaxseed along with exercise	6	65/54 \pm 16/1059

Results of One-way ANOVA for comparison of groups based on TNF- α and IL1 β , is shown in Table 2. For IL1 β , regarding that significance level is $p=0.002$, so there is significant difference between groups ($F=4.942$). LSD follow up test indicated that the significant difference in IL1 β mean, is only seen between control group and exercise group ($p=0.025$), control group and 10 mg/kg flaxseed along with exercise group ($p=0.003$), control group and 20 mg/kg flaxseed along with exercise group ($p=0.000$), 10 mg/kg flaxseed group and 10 mg/kg flaxseed along with exercise group ($p=0.019$), 10 mg/kg flaxseed group and 20 mg/kg flaxseed along with exercise group ($p=0.002$), and 20 mg/kg flaxseed group and 20 mg/kg flaxseed along with exercise group ($p=0.024$) ($\alpha \leq 0.05$). There were no significant difference between other groups ($\alpha \leq 0.05$). For TNF- α , regarding that significance level is $p=0.000$, so there is significant difference between groups ($F=21.171$). LSD follow up test indicated that the significant difference in TNF- α mean, is only seen between control group and exercise group ($p=0.039$), control group and 20 mg/kg flaxseed group ($p=0.039$), control group and 10 mg/kg flaxseed along with exercise group ($p=0.001$), control group and 20 mg/kg flaxseed along with exercise group ($p=0.000$), 10 mg/kg flaxseed group and 10 mg/kg flaxseed along with exercise group ($p=0.018$), 10 mg/kg flaxseed group and 20 mg/kg flaxseed along with exercise group ($p=0.000$), and 20 mg/kg flaxseed group and 20 mg/kg flaxseed along with exercise group ($p=0.000$), and exercise group and 20 mg/kg flaxseed along with exercise group ($p=0.000$) ($\alpha \leq 0.05$). There were no significant difference between other groups ($\alpha \leq 0.05$) (Table 2).

Table 2: one-way ANOVA

Parameters	variable	sum of squares	Freedom degree	Average square	F	Significance
TNF- α	Within groups	190370.139	5	38074.028	21.171	0.000
	Between groups	53952.167	30	1798.406		
	Total	244322.306	35			
IL1 β	Within groups	706216.889	5	141243.378	4.942	0.002
	Between groups	857371.33	30	28579.044		
	Total	1563588.222	35			

DISCUSSION

Findings of present study shows that both exercise and flaxseed oil are highly effective on reduction of TNF- α and IL1 β levels. Previous studies have indicated reduced, increased, and without alteration levels of TNF- α and IL1 β due to physical activity. The present study showed that aerobic exercise results to significant decrease in TNF- α and IL1 β levels that is in concordance with several previous studies.

In clinical studies, it is indicated that aerobic exercise for 12 weeks, decreases TNF- α level in patients with cardiac disability. Another study assessed the effect of exercise for 12 weeks on activity of cytokines in 28 patients affected by coronary artery disease (mean age of patients were 64 ± 7.1). Exercise program contained 45 minutes of aerobic exercise with 70-80% HRmax for 12 weeks. The results indicated that aerobic physical activity can significantly reduce TNF- α , IL1 β , IL-6, and CRP. In contrast, the level of IL-10, which is a cytokine inhibitory agent, significantly increased (Kargarfard et al., 2016; Signorelli et al., 2003; Tousoulis et al., 2003; Goldhammer et al., 2005; Adamopoulos et al., 2001; Ding et al., 2004; Wang et al., 2001; Mogharnasi et al., 2009). On the other side, another study indicated that aerobic exercises for 12 weeks results to increased insulin sensitivity in fat and overweight girls. However, no significant difference is showed in body weight and body fat percent, as well as levels of pro-inflammatory factors such as TNF- α , and CRP. Intensity, duration, and type of physical activity, are factors that can deeply effect on inflammation parameters.

In this study, due to the more useful effects of aerobic exercise on the VO₂max and the aerobic and anaerobic metabolism (Burgomaster et al., 1985; Burgomaster et al., 2008; Rodas et al., 2000), and because fats are more used than carbohydrates in these exercises as the fuel (Burgomaster et al., 1985; Burgomaster et al., 2008), and also the fat is one of the tissues with high secretion of-pro-inflammatory factors, therefore, the increase of using fats as the fuel and reducing the fat tissue of the body leads to lower secretion of pro-inflammatory factors (Ding et al., 2004; Wang et al., 2001; Mogharnasi et al., 2009; Adamopoulos et al., 2001; Signorelli et al., 2003; Tousoulis et al., 2003; Goldhammer et al., 2005; Kargarfard et al., 2016). Moreover, it is indicated that aerobic exercises can strongly stimulate cardiovascular and muscular compatibilities (Wenger & Bell, 1986; Wisloff et al., 2009), hypotension in fat people (Whyte et al., 2010), and improving cardiac preparation, endothelial function, insulin sensitivity, sympathetic activity parameters, and arterial intensity in cardiovascular patients (Ciolac, 2012). In the present study, flaxseed seed oil resulted in significant decrease in TNF- α and IL1 β levels. However, there is limited studies that assess the effect of flaxseed oil on TNF- α and IL1 β levels, which could be used for comparison to this study. While these studies did not assessed our studied factors, total results are in concordance with the present study that flaxseed oil results to decrease in cardiovascular involved inflammatory factors. Studies showed that flaxseed oil usage can reduce oxidative stress, and inflammatory factors in dialysis patients (Mirfatahi et al., 2016). Another study showed that flaxseed oil can effect on C Reactive Inflammatory Agent in fat people and decreases this factor (Ren et al., 2016). In this study, it is showed that different doses of flaxseed seed oil can have different effects on inflammatory factors, so that, in groups which received 20mg/kg body weight dose, in comparison to groups which received 10mg/kg body weight dose, had more effects on decreasing inflammatory factors. In the other word, 20 mg/kg flaxseed oil resulted in better and greater recovery in comparison with 10 mg/kg dose.



There are few studies regarding simultaneous effect of aerobic exercises and flaxseed oil on inflammatory factors. The only study in 2012 –which its results were in concordance with our results- has assessed simultaneous effect of physical exercise and flaxseed oil, which indicated that this simultaneous effect can significantly decrease levels of TNF- α and IL1 β in ischemic rats (Nounou et al., 2012). It is probable that high basic levels of the parameters in ischemic rats resulted that the effect of exercise and nutritional interventions to be significant; however, these results were in concordance with our results. By assessing different studies, the possible mechanisms of this decrease or increase can be understood. Moderate and routine endurance exercises, results to reduction of concentration of adhesion molecules, via reduction of sympathetic stimulation and enhancement of anti-inflammatory cytokines. During endurance exercises, endocrine system increases fat oxidation (lipolysis), via increasing epinephrine, norepinephrine, GH, and cortisol, also with increasing in call and use of free fatty acids to generate energy during activity, the energy need of muscles will be provided and the body fat mass decreases. Aerobic exercise has been associated with increased fat oxidation and reduced body fat mass, which is a mechanism for reducing inflammatory mediators and sticky molecules. As it is said, regular endurance exercises inhibits secretion of TNF- α and IL1 β inflammatory mediators from fat tissue via reduction of sympathetic stimulation and anti-inflammatory cytokines enhancement (IL-10); as a consequence, concentration of adhesion molecules decreases. Studies that used intense exercises, makes the possibility that intense exercise will result in muscle damage, and levels of inflammatory parameters have increased due to muscular damage. It also seems that studied that reported no alteration in the levels of inflammatory agents, did not use enough exercise intense. The present study, showed the reduction of inflammatory mediators (TNF- α , and IL1 β) during intense interval exercises; however, there is the possibility that this high intensity during 10 weeks, resulted in compatibility of rats and decreasing TNF- α and IL1 β . Totally, many factors such as physiological and metabolic factors that can affect metabolism include lower muscle mass, higher fat, different fat distribution and serum lipid basic levels, and other factors including gender, health status, race, diet, weight, BMI, exercise intensity, exercise volume, exercise duration, exercise type, number of people, differences in energy consumption, activity level outside the exercise program and calorie intake can widely effect on the response of IL-1 and TNF- α inflammatory mediators to exercises. So that, in the interpretation of results should be discussed more carefully (Sanadgol et al., 2012; Papageorgiou et al., 2011). Recent studies indicated that flaxseed seed oil results to reduction of cholesterol, stabilization of blood glucose, prevention of osteoporosis, helping in weight loss, and especially improvement of immune system, prevention of cancer, and improving memory and intelligence (Deng et al., 2011; Chytilova et al., 2013; Chytilova et al., 2014; Green et al., 1986; Tanna et al., 2012; Tuluze et al., 2012; Williams et al., 2006). It is also reported that flaxseed seed oil can reduce the risk of cardiovascular diseases (Han et al., 2015). Important functions of flaxseed oil are related to its omega 3 and omega 6 contents. However, some studies showed that omega 3 fatty acids has no effect on inflammatory mediators (TNF- α and IL1 β). The cellular mechanism of flaxseed oil in reducing inflammatory factors and ultimately reducing cardiovascular diseases is probably due to the effect of omega-3 on the gene expression of peroxisome proliferator-activated receptor (PPAR). It is showed that omega 3 fatty acids inhibit NFkb nuclear factor via increase in PPAR, which eventually inhibits secretion of inflammatory



and pro-inflammatory cytokines. In the other word, using supplements containing omega-3 fatty acids via inhibition of factors involved in secretion of inflammatory and pro-inflammatory, prevents vascular inflammation agents, including intracellular adhesion molecules (ICAM-1) and vascular adhesion molecules (VCAM-1), and reduces inflammation, and ultimately reduces the diseases caused by Inflammation, including cardiovascular disease (Chen et al., 2005; Wang et al., 2011; de Winther et al., 2005; Jaudszus et al., 2008; Ridker et al., 2000; Spittle et al., 2001). Omega 3 fatty acids of flaxseed oil also directly reduce inflammatory cytokines production by mononuclear cells; however, its mechanism is not known, yet (Li et al., 2005).

When inflammatory cytokines such as TNF- α bind to their receptors on the membrane of vascular endothelial cells, phosphorylate the inhibitor of nuclear factor kb (I-KB) that detached it from a transcription factor named nuclear factor kb (NF-KB) placed in cytoplasm. Afterwards, NF-KB goes to nucleus and via binding to different genes such as ICAM-1 and VCAM-1 increases their expression and as a consequence their synthesis. Omega 3 fatty acids prevent phosphorylation of I-KB and its separation from NF-KB; so, reduces expression of ICAM-1 and VCAM-1 genes in endothelial cells. This event reduces number of ICAM-1 and VCAM-1 proteins on the endothelial cell membrane and their concentration in blood (Ziccardi et al., 2002; Ding et al., 2004).

CONCLUSION

Overall, results of the present study showed that aerobic exercise along with usage of flaxseed seed oil for 8 weeks, by reducing inflammatory agents reduces diseases caused by inflammation, including cardiovascular disease. Aerobic exercises and usage of flaxseed seed oil which is full of omega 3 and omega 6, in long term, can prevent inflammatory diseases such as cardiovascular disease, by reducing inflammation. Therefore, regarding effects of these two interventions (exercise and flaxseed oil) on reduction of inflammatory agents in cardiovascular diseases, it is recommended to do aerobic exercises and use flaxseed seed oil to prevent and treat cardiovascular diseases.



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