The effect of aerobic training and consumption of L-carnitine supplements on HMG-CoA reductase and LDL receptor in the liver of male wistar rats toxicated by boldenone

Behnam Bagherzadeh Rahmani[1], Asieh Abbassi Daloii[1*]

1. Department of Exercise Physiology, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran

***Corresponding author:**Tel: +98 9111274366 Fax: +98 -
Address: Department of Physical Education and Sports Sciences, Islamic Azad University, Ayatollah Amoli Branch, Amol, Iran
E-mail: abbasi.daloii@gmail.com
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Abstract

Introduction: The aim of this study was to investigate the effect of aerobic training and consumption of L-carnitine supplements on HMG-CoA reductase and low density lipoprotein receptor (LDL-R) in the liver of male Wistar rats toxicated by boldenone.
Materials and methods: In this clinical study, 30 male Wistar rats aged 12 weeks (weight 195±7.94g) were randomly divided into five groups: control, no-treatment, boldenone (5mg per kg), L-carnitine and L-carnitine + training groups with six rat in each group. The moderate intensity endurance training program (50-55% of maximal oxygen consumption) performed for 6 weeks and 5 times a week. Injection once a week, on an appointed day, and in the quadriceps and hamstring was conducted in depth. After anesthesia, biopsy in aliquots was prepared. The HMG-CoA reductase and LDL-R expression in the samples was measured by Real-Time-PCR and the quantification of gene expression levels was calculated using the formula $2^{-\Delta\Delta ct}$ then analyzed by One-way ANOVA and post hoc Scheffe at $P<0.05$.
Results: The results showed that aerobic training and supplementation with L-carnitine had significant effects on HMG-CoA reductase and LDL-R in the liver of male Wistar rats intoxicated by boldenone (P=0.0001). The results showed that the expression of HMG-CoA reductase in training-L-carnitine group was significantly lower than the control group (P=0.0001). The expression of LDL-R in training-L-carnitine and L-carnitine group increased significantly compared to control group (P=0.0001).
Conclusion: According to the findings, it seems to the supplementation with L-carnitine alongwith regular aerobic training modulate the biosynthesis of cholesterol in liver tissue.

Keywords: Aerobic training, Boldenone, L-carnitine, HMG-CoA reductase, LDL receptor, Wistar rats

Introduction

Androgenic anabolic steroids, including testosterone and other endogenous androgenic hormones and synthetic materials made with these compounds has been linked with doping agents that have been well identified and sport communities. Abuse of these factors for health purposes in non-competitive athletes, bodybuilders and even non-athletes leads to a lot of concerns (1-3). The steroid boldenone is derived from testosterone that displays an anabolic and androgenic strong actions in

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order to improve growth (4). Although Boldenone has dual effects on humans, the effect of this steroids on the structure and functions of different tissues is unknown.

The prime function of low density lipoprotein receptor (LDL-R) is removing the highly atherogenic low density lipoprotein (LDL) particles from blood circulation. Since the liver contains about 70% of total LDL-R in the body, LDL-R activity in the liver is an important factor in regulating the LDL levels of plasma cholesterol. The analysis suggests that anabolic-androgenic steroids impaired lipoprotein profile. The most prominent changes include increased levels of LDL and decreased high-density lipoprotein (HDL) (5). Studies have shown that high doses of testosterone may exert adverse effects on cholesterol metabolism (6). Cholesterol is primarily synthesized in the liver and its synthesis rate-limiting factor is reduction of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-COA) to Mevalonate-a catalyzed reaction by HMG-COA reductase. HMGCoA reductase is an enzyme that converts acetate into cholesterol or in other words, it controls the biosynthesis of cholesterol in the liver cells. Normally, transcription of HMGCoA-R in mammalian cells is suppressed by cholesterol derived from the degradation of LDL by the LDL-R (6). LDL-R is another receptor on the cell surface that mediates consumption and catabolism of plasma cholesterol. The prime function of these receptors is removing highly atherogenic LDL particles from circulation. Since the liver contains about 70% of total LDL-R in the body, the liver LDL-R activity is considered an important factor in regulating the plasma levels of LDL cholesterol (7).

There is little information on the effects of exercise training on cholesterol biosynthesis. The main findings in human studies support the fact that exercise training improves fat metabolism and cholesterol, increases plasma HDL levels and the simultaneous reduction in LDL cholesterol and triglyceride levels (8, 9). In animals, the positive effects of exercise training on lipid metabolism and cholesterol were shown by Ramachandran et al. They reported a 50-percent reduction in atherosclerotic lesions in mice that had slipped and weakened LDL-R. They suggested that exercise has several desirable effects including maintaining the integrity of endothelial cells, reduction of inflammation and oxidative stress (10). Similarly, Matsumoto and colleagues reported that exercise in mice with LDL-R weakening of the aortic valve prevents sclerosis. They suggested that exercise has many positive effects including maintaining the integrity of endothelial cells, reducing inflammation and oxidative stress (10).

Reduction in aortic lesion size has been reported by Meissner and colleagues after 12 weeks of training in mice with deficient LDL-R activity (11). Ngo Sock et al. reported that it does not seem that 8 weeks of training to have any effect on HMGCoA-R (12). Meissner et al. also reported the increase in the proportion of lanosterol to cholesterol in mice after two weeks of optional training that indicates an increase in the biosynthesis of cholesterol. However, they reported reduction in HMGCoA-R after 12 weeks of optional training in LDL-R in LDL-R deficient mice. In general, it is not clear that the biosynthesis of hepatic cholesterol with training will change or not. Meissner et al. reported that molecular pathways involved in the development of the effect of training on plasma lipids is not well defined. In addition, analysis of the effects of exercise training on molecular components of cholesterol metabolism in the liver by a variety of used animal models is complex.

Studies have shown a decrease in carnitine concentrations in blood and tissues in hyperlipidemia. Treatment with L-carnitine can lead to normalization of carnitine concentrations, plasma cholesterol, and triglycerides (13). L-carnitine (3-hydroxy-4-N-trimethylaminobutyrate) is a biologically active form of carnitine, an

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endogenous branched amino acid which plays a vital role in the production of unnecessary energy. This supplement passes free fatty acids into the mitochondria resulting in an increase in the preferred substrate for oxidative metabolism in tissues (14). L-carnitine inhibits the progression of atherosclerotic lesions due to lipid-lowering antioxidant effects. Studies also show reduction in total cholesterol and triglycerides in patients taking L-carnitine (15). However, few studies that have examined the effect of L-carnitine on HMG-CoA reductase and LDLR and the results were often contradictory.

There are numerous reports on studies of the side effects of anabolic steroids on various organs, including the cardiovascular and liver damage, as well as impaired lipid profile, which may increase the risk of cardio - vascular diseases (6,16). According to the above mentioned points, no research was conducted on the effects of anabolic boldenone steroid along with aerobic exercise, and L-carnitine on the metabolism of cholesterol in the liver. On the other hand, since the androgenic anabolic steroids may affect the homeostasis of cholesterol by increasing the expression of HMGCR, thus it is very important to enhance the perceived influence of anabolic androgenic steroids side effects in order to find the necessary steps for the care and treatment of athletes and people that abuse AAS.

Therefore, due to the negative effects of uncontrolled anabolic steroids hormones on the body, and especially disturbances in lipid profiles in the body, we can investigate the effect of influential supplements on the levels of lipid profile to reduce the devastating effects of this hormone. For this reason, finding food supplements that help to protect the body especially the liver against damage caused by anabolic androgenic steroids is of utmost importance. However, according to surveys and studies, little research was done on the effect of L-carnitine supplementation and exercise training on lipid profile in liver tissue. From this perspective, the findings are very important. This study aims to examine the effects of aerobic training and supplementation with L-carnitine on HMG-CoA reductase and LDL receptors in the liver of male Wistar rats intoxicated with boldenone.

Materials and methods

The statistical community of the study included male wistar rats from Physiology College of Shahrood University and 30 male wistar rats with the age of 12^{th} weeks with the initial weight of 195±7/94 were selected as statistical samples. The sample of this research was accomplished using targeted sampling method according to weight and age. Then, the samples were randomly divided into 5 groups: control, no-treatment group, boldenone (5 mg per kg), L-carnitine, and L -carnitine + training with six rat in each group. One of the groups used only carnitine (100 mg per kg). Other group used carnitine and did training. Without treatment had no activity or extract taking since beginning of injection and training.

Study groups were divided into rodent's special cages for rodents made of PVC with steel mesh cap and the floor was covered with clean wood chips. The room temperature was 22± 4.1°C with humidity of 65 to 75 percent. The animals under study had a 12-hour sleeping and awakening cycles with access to water and foods. They were fed by compressed special food made by Gorgan Factory and given refined civil water offered in PVC containers. For prescribing and drug injection of insulin graduated syringes were used. The injections were done once a week, at 11 am and on an appointed day of the week. The injections were administered deeply in the posterior thigh muscles. The control group received the physiological solution or a solution of normal salin or sodium chloride 0.09.

Procedure for intake of L-carnitine supplementation: The experimental groups during the intervention period

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received 100 mg of L-carnitine as gavage per kilogram of body weight.

Aerobic training protocol: In the present study, intermediate training intensity (50-55% of maximal oxygen consumption) and physiologically effective exercises were used. The training groups were given treadmill exercises with the average intensity of 5 days a week for the duration of 6 weeks. Speed and duration of treadmill exercise gradually increased from 10 meters per minute for 10 minutes in the first week, 10 meters per minute for 20 minutes in the second week, 14-15 meters per minute for 20 minutes for the 3rd week, 14-15 meters per minute for 30 minutes in the fourth week finally to 17-18 meters per minutes for 30 minutes in the fifth week. In order to achieve consistency of results in uniform mode, all training variables were kept constant in the final week. To stimulate the rats to run, sound stimuli (hitting the treadmill) were used. At the first session, electric low-voltage stimulus along with sound stimulus were used. After conditioning the rats to running, at the other sessions only sound stimuli were used for ethical purposes.

Sampling procedures and measuring changes in gene expression in liver tissue: At the end of the study after 56 days, the animals kept fasting for 12 hours. The samples were then weighed and anesthetized for sampling. Anesthesia was done using glassy chamber (desiccator), containing cotton soaked in chloroform a product of Merck of Germany. After 40 to 50 seconds animals were in anesthesia. After the anesthesia the animal was fixed on the rodent surgery board, autopsy was performed and liver tissue was immediately removed. In this research, ethical issues about laboratory work on animals including the availability of water and food, proper maintenance and non-refoulement training were considered. All experiments were performed in accordance with the policies of the Helsinki Agreement.

Measuring the gene expression of HMG-CoA R and LDL-R was assessed by Real time - PCR technique and analyzed after the quantification of gene expression values using the formula $2^{-\Delta\Delta ct}$. The considered Primer genes and beta-actin were designed and studied by Allele ID and MEGA 6 software. The specificity of the primers for the target genes was investigated by the BLAST program. In this study, GAPDH gene was used as an internal control. The sequence of primers used in this study are presented in the Table 1.

Table 1. The primer sequences of the variables under study

Gene name	Primers	Sequence	Length amplicon
HMG-CoA reductase	Forward	5'-GGCTTGGCCTCCATTGAGATCC-3'	104 bp
	Reverse	5'-ATACAGATTGTAAGTGTCACTGT-3'	
LDL receptor	Forward	5′-CCTGCTCCTGGCTGCTGCCGG-3′	123 bp
	Reverse	5′-CTCTGGGGACTCATCGGAGCC-3′	

LDL-R; low density lipoprotein

Statistical analysis

After ensuring the normal weight distribution with the Kolmogorov - Smirnov test, Levene test was used to check homogeneity of variances. One-way analysis of variance test was used for changes within the group and Scheffe post hoc test was used to assess differences between groups. All statistical operations were done using SPSS version 22, the considered significance level was $P< 0.05$.

Results

Data analysis showed that there is a difference between the average of HMG-CoA reductase gene expression in the male Wistar rats in groups of research, (P=0.0001). Scheffe test results showed

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changes in gene expression of HMG-CoA reductase in Boldenone supplement group significantly increase compared with control and no-treatment groups (P=0.0001). HMG-CoA reductase gene expression changes in Exercise-L-carnitine group was significantly lower compared with the control group (P=0.0001).

Changes in HMG-CoA reductase gene expression in the group of L-carnitine and L-carnitine-training was significantly lower than the Boldenone Group (P=0.0001). Changes in HMG-CoA reductase gene expression in Exercise-L-carnitine group was significantly lower compared to the L-carnitine group (P=0.0001) (Figure 1).

Data analysis showed that there are differences between the means of LDL-R expression in male Wistar rats in different research groups (P=0.0001). Scheffe test results showed that changes in the expression of LDL-R in training - L-carnitine and L- carnitine significantly increased compared to control and no-treatment groups.

Also, the results showed that changes in the expression of LDL-R groups significantly reduced than the control and boldenone group (P=0.0001). Changes in the expression of LDL-R in L-carnitine and Training-L-carnitine was significantly higher compared to boldenone group (P=0.0001). Changes in LDL-R expression the group of training -L-carnitine was significantly higher compared to L-carnitine group (Figure 2).

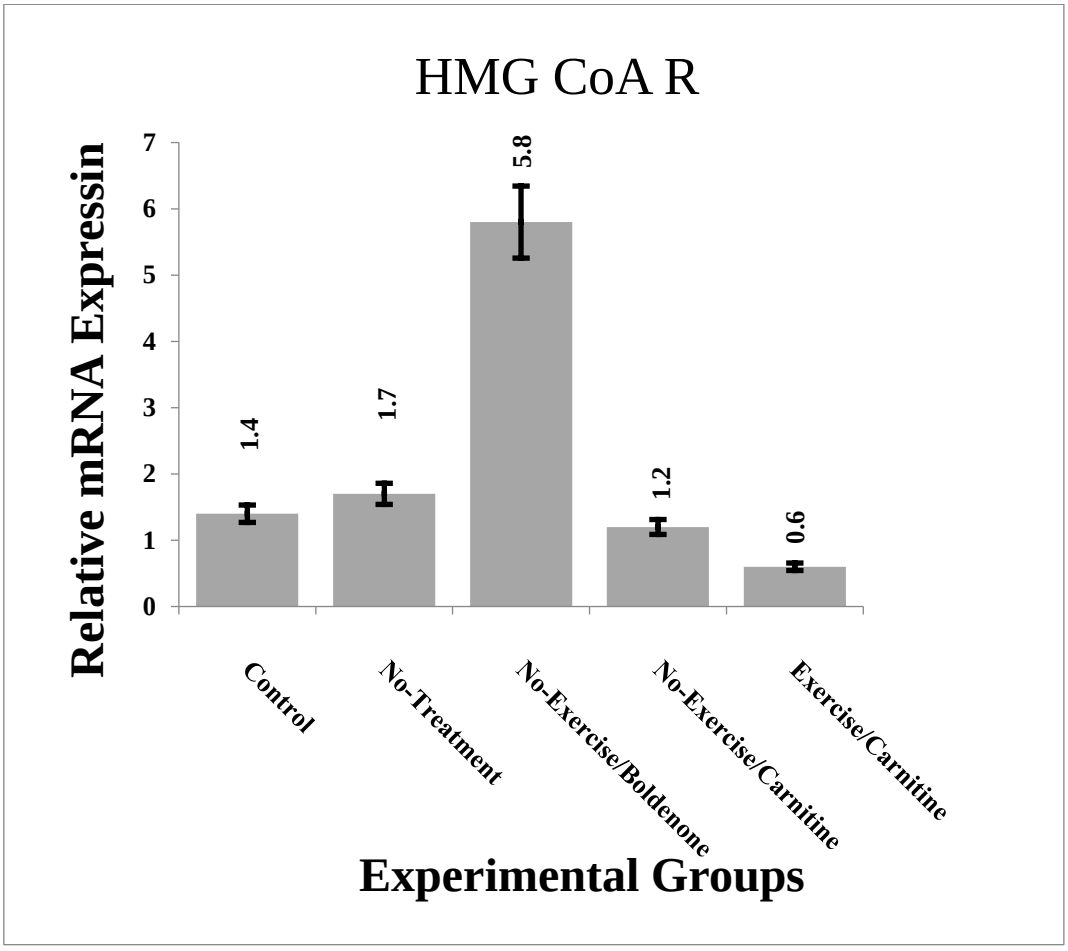


Figure 1. Changes in the expression of HMG-CoA reductase (HMG-CoA R) gene in male wistar rats in different groups.

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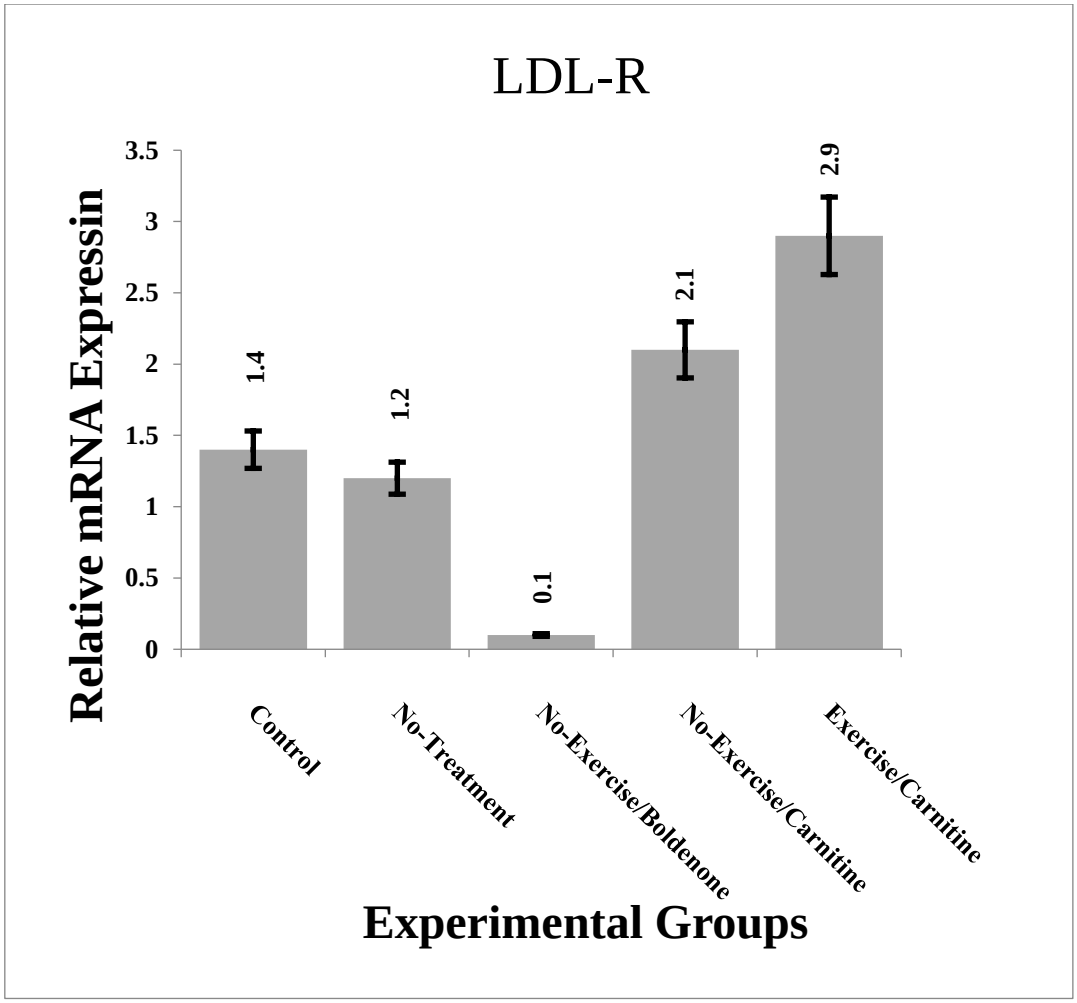


Figure 2. Changes in the expression of low density lipoprotein receptor (LDL-R) in male wistar rats in different groups.

Discussion

The results showed that aerobic training and supplementation with L-carnitine has significant impact on HMG CoA reductase and LDL-R of liver tissue of male Wistar rats intoxicated with boldenone. Changes in expression of HMG CoA reductase in the liver tissue of the supplement groups of boldenone and exercise- boldenone significantly increased compared to control group. Also, changes in expression LDL-R in liver tissue of the boldenone supplement group and exercise-boldenone supplement group was significantly lower compared to control group. Cholesterol synthesis is associated with HMGCR activity and it has been shown that testosterone can affect the expression of this enzyme. Garevik et al. (2012) showed that high doses of physiological testosterone prescription lead to HMGCR expression (6). These observations were confirmed by the results of experiments with HepG2 cells exposed to 1 micro molar of testosterone (17).

The concentration in a wide range of levels have been achieved after administration of testosterone and was associated inducing transcription of HMGCR gene (17). In addition, it has been shown that administration of anabolic androgenic steroids (testosterone and nandrolone) for 14 days' results in upregulation of gene expression in HMGCR adrenal. A baseline serum concentration of testosterone in the study by Garevik et al. (2012) and some other similar studies, that included age, gender and race, was 5 nanograms per milliliter. In a study, it has been shown that two days after administration of

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testosterone serum, testosterone levels increase up by 200% (17, 18). Consistent with the findings, Garevik et al (2012) stated that anabolic androgenic steroids may affect cholesterol homeostasis via increased expression of HMGCR (6). Garevik et al. (2012) examined a single dose of testosterone on cholesterol synthesis and HMGCR expression in healthy volunteers two days before and fifteen days after the administration of 500 mg of testosterone. Their results showed that total cholesterol levels significantly increased by 15% two days after injection of testosterone. In addition, HMGCR mRNA and protein expression were induced by testosterone. The results also showed that boldenone supplement significantly increases HMG-CoA reductase gene expression in the liver of rats after six weeks (6). In addition, Ngo Sock et al. (2014) in a study determined the effects of exercise training on hepatic gene expression of key molecules involved in cholesterol metabolism. Their results showed that training has significant effect on LDL-R gene expression and liver HMGCoA-R. Exercise training significantly reversed the effects of ovariectomy on obesity, plasma triglycerides and total cholesterol. Their findings revealed that Hypercholesterolemia in rats is related to decreasing hepatic LDL-R gene expression. Thus, the results of this study is consistent with the findings of Ngo Sock et al. (2014) and Garevik et al (2012) on the point of increase in the HMG-CoA reductase gene expression in liver tissue after a period of supplementation.

Several reports have been released on the effects of anabolic androgenic steroids on human lipoproteins in the past 25 years. The results indicated that anabolic androgenic steroids lead to a significant reduction in serum HDL and increase in LDL levels (5, 19). Some studies have shown that high doses of anabolic androgenic steroids in frequent physiological administration are associated with increased levels of total cholesterol (20, 21), while some studies have reported conflicting results (22). The reasons for the observed difference in effects of administration of anabolic androgenic steroids on the total cholesterol may be due to study design and methods, sampling time, the type of used androgenic anabolic steroids and injection site. However, the most important cases involve the use of different doses or chronic and acute use. Molecular mechanisms of adverse effects of anabolic androgenic steroids on lipoprotein profile has not been thoroughly examined. It is believed that androgenic anabolic steroids apply some of their effects on cholesterol by stimulating HDL liver degrading enzymes namely the liver triglyceride lipase (HTGL) (22). The 143 up to 232 percent increase in HTGL activity by the abuse of anabolic steroids androgenic has been observed (23). However, in this study HTGL activity levels were not measured.

In addition, the inducing mechanisms of HMGCR transcriptional regulation and the physiological consequences were properly dealt and need further research. It is known that high cholesterol levels in the leads to negative feedback in cholesterol synthesis at level of transcription. This may explain time-dependent response observed in HepG2 experiments, for example the expression of normal mRNA HMGCR or even negative adjustment after 24 hours of treatment with testosterone (24, 25).

Results of the present study also showed the changes in the expression of HMG-CoA reductase in the liver of male Wistar rats in exercise- L-carnitine group was significantly lower than the control group. The results indicated that that changes in the expression of LDL-R in L-carnitine and exercise- L-carnitine groups significantly increased compared to the control and sham groups. Dyslipidemia progress is influenced by several factors including carnitine deficiency, which leads to disruption of the metabolism of fat. Carnitine can significantly lower levels of

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plasma lipids and tissue (26). Few studies were done on the impact of Carnitine the HMG-COA reductase and LDLR. Mondola et al. examined the effect of carnitine on the metabolism of cholesterol and the activity of HMG-COA reductase in the liver cells of mice and showed that they showed that L-carnitine can inhibit the activity of HMG-COA reductase as well as increase the connection of LDL to the liver cells (27). However, Lee et al. (2016) showed that supplementation with LC at a dose of 1000 mg per deciliter increase the levels of HDL-C and Apo-A1 and slightly reduces the triglyceride levels, but no changes were observed in other lipids in the patients. They stated that the lipid lowering effect may be related to its antioxidant abilities (28).

In addition, the impact of exercise training on cholesterol biosynthesis of liver tissue is examined in a few studies. By the same token, Wei et al. (2005) showed that the expression of mRNA SR-BI and LDL receptor levels in the liver of mice increase after 2 weeks of aerobic training (29). Cholesterol level regulatory system is located in the membrane of the endoplasmic reticulum to maintain cholesterol homeostasis. In fact, the regulatory system acts in response to the amount of cholesterol inside the cell and at the transcription level and gene expression is increased at the time of intracellular cholesterol-lowering and this in turn leads to increased expression of three genes LDL-R, HMG-COA reductase and PCSK-9 (30, 31). Increased expression of LDL-R lead to harvest more plasma cholesterol and thus the increase in the clearance of LDL-C. More expressions of HMG-COA causes increases in the cholesterol synthesis inside the cell, but increased PCSK-9 synthesis leads to the decomposition of LDL-R and thus decreased clearance of LDL-C and increased LDL-C. Recent action contrasts two mechanisms so that LDL-R performance overcomes PCSK-9 performance and overall increases LDL-C (32, 33).

Finally, the results show that the expression of LDL-R in Exercise-L-carnitine-boldenone group did not differ compared to the control group. Argüello and colleagues showed that L-carnitine supplementation has no effect on increasing fat oxidation, increased aerobic performance, as well as other metabolic factors at the time of aerobic training (34). Furthermore, then study by Eizadi et al. showed that L-carnitine supplements do not cause changes in lipid metabolic variables levels during submaximal exercise training and will not improve endurance performance. In studies conducted in this scope, in some cases different results were obtained and reports are unclear (36). The inconsistent results maybe be due to different levels of L-carnitine supplementation or different methods. In some cases, it may be due to different circumstances of the subjects, age, sex and level of physical training (37). The paradox in research can be attributed to factors including the type of exercise, intensity, duration and training period. It seems that, the contradiction between the findings of various studies on L-carnitine supplementation during submaximal endurance training is due to the difference in methodology and fitness tests as well as L-carnitine intake duration, intensity or volume of the activity that needs further studies to comply with all aspects of metabolic variables and simultaneous measurement of fat.

LDLR activity mechanisms at both level of transcription and post-translation are discussed. Studies have shown that the LDLR activity in both transcriptional and post-translational level can be adjusted. LDLR post-translational regulation is moderated by PCSK9, which can be intracellular, extracellular and direct complex for destruction due to lysosomes connected to the LDLR proteins (38, 39).

At the level of transcription, LDLR is regulated by SREBP-2, which is connected to the SRE-1 in the LDLR gene promoter. SREBP-2 positive regulation of transcription ultimately leads to increased

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clearance of LDL from the SREBP-2 in the blood stream (40). However, this LDLR transcriptional regulation is inconsistent because SREBP-2 also increases the PCSK9 transcription which in turn increases the LDLR protein degradation in the liver and thus limits the absorption of LDL particles in the plasma. Thus, the two opposing effects on plasma cholesterol levels by similar metabolic signals begin. As a result, a significant induction of Pcsk9, which moderate the functional LDLR protein degradation, could be a possible explanation for the reduction of liver LDLR protein in rats after the training period. Intensity and duration of training may stimulate the expression of genes involved in the metabolism of cholesterol in the liver. Previous studies have shown that 8 weeks of treadmill exercise training has no effect on the expression of genes involved in cholesterol metabolism in the liver of the ovariectomized rats (12). It is likely that exercise training regulates plasma and liver cholesterol levels with various mechanisms such as increased excretion of cholesterol through bile acids. There is no evidence of factors affecting cholesterol metabolism in the liver at molecular level.

Diet affects free cholesterol in the liver and lead to a change in the activity of cholesterol reductase synthesis regulating enzyme namely HMG-COA reductase. The first compensatory response to the concentration of dietary cholesterol is regulating the activity of HMG-COA reductase (41). In addition, when the concentration of cholesterol in the liver is reduced, HMG-COA reductase is positively regulated. The results of the studies indicate that there may be a liver threshold in the concentration of cholesterol and a regulatory response to cholesterol synthesis with the increased activity of HMG-COA reductase (42).

L-carnitine supplementation and exercise training can reduce total cholesterol. In the study by Pataly and colleagues oral L-carnitine supplement and aerobic training were prescribed and eating low-calorie diet led to lower cholesterol led (43). Several studies have been conducted on the effects of supplementation with L-carnitine on fat percentage and body mass index with given the amount of supplementation, subjects and methods of research had different results. The limitations of this study include lack of measurement of cholesterol biosynthesis of other related factors. Measurement of biomarkers such as cholesterol Activity like Lathosterol can reveal the effects of prescribing higher doses of physiological testosterone in disrupting the metabolism of cholesterol in the body.

Conclusion

The results showed that aerobic training and supplementation with L-carnitine has significant impact on CoA reductase and LDL-R in the liver of male Wistar rats toxicated with Boldenone. Changes in HMG-CoA reductase expression in liver tissue of male Wistar rats in HMG in L-carnitine-training group was significantly lower than the control group. Changes in the expression of LDL-R in groups L-carnitine and L-carnitine-training groups were significantly higher compared to control group. According to the findings, supplementation with L-carnitine along with regular aerobic exercise training moderate biosynthesis factors of cholesterol in liver tissue.

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Conflict of interest

The authors declare that no conflict of interest exists**.**

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