# The Effect of 6 Weeks of Endurance Training on the Expression of Hepatic ABCA1 in Male Wistar Rats

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**Abstract:** Increasing the HDL cholesterol level by 1 mg may reduce the risk of cardiovascular disease by 2 or 3%. This protective effect of HDL is due to its role in the process of reverse cholesterol transport (RCT). RCT process consists of removing excess cholesterol from peripheral cells to the liver to exert as bile. The first step of RCT mediates by ABCA1. Dysfunction of ABCA1 in human and animal model leads to severe decrease of HDL level and incident of arteriosclerosis while the over-expression of this gene has opposite effects. So it seems that knowing the activator of this gene may have beneficial effect in prevention of cardiovascular diseases. To examine the effect of exercise training of the expression of hepatic ABCA1, 10 male wistar rats were subjected to treadmill running for 6 weeks, 5 days a week, 90 min with 26 m/min during each training session. The results of this study clearly showed the expression of hepatic ABCA1 following the 3 weeks of endurance training. So it seems that one of the positive effects of exercise training in prevention of cardiovascular diseases may be the expression of ABCA1, which is the first key step in reverse cholesterol transport.  
   
**Key words: ABCA1 • Endurance Training • Reverse Cholesterol Transport • HDL**

**INTRODUCTION**

Coronary cardiovascular disease is one of the death factors in the world. The disease has a direct relationship with the increase of plasma low lipoprotein (LDL) and very low lipoprotein (VLDL) and a reverse relationship with the high lipoprotein (HDL-C) [1-8]. Although LDL has anti-oxide and anti- inflame effects [5] but the general belief is that HDL performs its protective role from cardiovascular diseases through reverse cholesterol transport [2, 6, 9-11]. Reverse cholesterol transit (RCT) process consists of removing excess cholesterol from peripheral cells such as macrophages of artery wall and return them to the liver and changing to HDL [3-4, 12-13].  
   
**Recent Studies Suggest the Rct Process as Follows:**

1. Cholesterol exert from the cells on Free-lipidated or poorly-lipidated Apolipo-protein A-I (Apo A-I). This process is mediated by ABCA1 which leads to the formation of Pre Beta HDL [6].
2. Excess cholesterol exit leads to the formation of Pre Beta HDL and larger HDL flat particles.
3. Cholesterol estriphization through Listin Cholesterol Acyl Transferase (LCAT) which leads to the formation of circular HDL.
4. HDL maturation i.e. formation of larger HDL particles through absorption and estriphization of excess cholesterol from other lipoproteins or through joining to smaller HDL particles.
5. Mature HDL form change by cholestril Ester Transfer Protein (CETP) phospho-lipid transfer Protein (PLTP), liver lipase and Scavenger receptor type BI (SR-BI) through formation of smaller HDL particles and minimally-lipidated A-I apolipo proteins [13-14].

The role of ABCA1 as the issuer of cell fat declared when it was discovered that this gene is a deficit gene in Tangier patients [15-18]. The Tangier patient has very low HDL in the absence of ABCA1 genes and is not able to exert cholesterol from the cell to the apo A-I; consequently, the cholesterol ester accumulates in most of the cells especially in their arteries [19].  
  
Early Arteriosclerosis is another side-effect of the disease. Beside human models, the dysfunction of ABCA1 in the rats also leads to the same side effects like those of Tangier disease [20].

Disorder in the ABCA1 gene of the Wisconsin hypo alpha mutant (WHAM) model (the only known natural animal model with the auto HDL scarcity) also leads to the decrease of the HDL and Apo A-I up to 95% [21]. On the other side, over-expression of the ABCA1 gene in the transgenic rats leads to the meaningful decrease of the size and complication of the arteriosclerotic damages, excess cholesterol exert from the cell and at last increase of plasma HDL amount and composition [22-26]. The results of these studies clearly show that the ABCA1 function has a key role in the reverse cholesterol transfer. Therefore, the attempt to understand these gene activators may be very useful for the prevention of arteriosclerosis.

Although the studies have shown that physical activity can lead to the amelioration of some key processes in the reverse cholesterol transfer procedure like the increase of HDL amount and composition [27], excess cholesterol exert from the cell [28], increase of formation and the size of Apo A-I [29-30], increase of plasma Pre Beta HDL [31-32] and increase of LCAT enzyme activity [29, 33-34] but up to now, no research is undertaken to investigate the effect of endurance training on the ABCA1 gene expression which is the first step in the reverse cholesterol transfer.

With regard to the point that no research is undertaken to investigate the effect of endurance training on the ABCA1gene expression, the present research investigates 6 weeks of endurance training on the expression of Liver ABCA1 gene.

**MATERIALS AND METHODS**

**Animals (Rats):** 10 white-race wistar rats were bought from Iran Pastor Institution. The rats were kept in especial cages under controlled conditions of light (12 hours brightness, 12 hours darkness), temperature (23±1 degree centigrade) and humidity (50±3%) in the animal house of Tarbiat Modarres University. The rats had freely access to the standard water and food and only one person changed their place or manipulated them during the research. After one week of acquaintance with the laboratory atmosphere and manipulation by human being, they were randomly divided in to two homogenous groups of experimental and control based on their weight.

**Research Procedure and Exercise Plan:** An experimental research with two groups of control and experimental is undertaken. The experimental group's endurance started with the severity of 15 meters per minute and as long as 10 minutes each day and finally reached the severity and final duration of 26 meter per minute as long as 90 minute by the gradual increase of 1 meter per minute and 7 minute 15 seconds each day [35]. Then, the rats continued with the same severity and duration for 6 more weeks, 5 sessions per week.  
It is worth mentioning that the endurance is estimated as a moderate endurance equal to the 70% of the outmost consumed oxygen [36-41].

The control group walked on a treadmill for 10 minutes with the speed of 12 meter per minute for three sessions per week to keep all conditions such as manipulating the rats by the researcher the same for both groups and the only difference of experimental and control group was in the endurance training.

24 hours after the last endurance training, the rats became unconscious by injecting peritoneum composed of ketamine and xylosin while they were hungry for a complete night (14 hours of being hungry). The liver tissue was immediately cut and transferred to the micro tube and was place in the liquid nitrogen. Then, the frozen tissue was put in the -80 freezer for mRNA delivering.  
   
**MRNA Delivering and Investigating the Expression of Gene by RT-PCR:** 50 mg of the frozen liver was homogenized and powdered to be used for mRNA delivery. The RNA was protected and cut by Guanidinium Thiocynate method and in order to separate mRNA, Roche Co. RNA delivery kit which is covered by Oligo (dT) with suitable quality and high purity level magnetic particles that are able to separate mRNA were used according to the Co. instructions. 0.5 microgram mRNA was used from per rat to synthesize the first c DNA string. In the present research, Oligo (dT) Primer that is the Ploy A tails complement in the mRNA was used while the temperature was 42 degree centigrade for 1 hour. The related kit was bought from German Fermentase Company. The relative level of mRNA of the ABCA1 gene in the muscle was measured by the semi quantitative RT-PCR method. This method was done with the help of especial ABCA1 primers including:

**ABCA1-forward:** 5-CGT CCT CCT TGT CAT CTC TG-3

**ABCA1-Reverse:** 5-TAA CTT TCT TTC ACT TTC  
TCG TC-3 which multiply a piece of 237 pairs in a gene. Especial primers of B-action were used to control the gene multiply. These primers include:

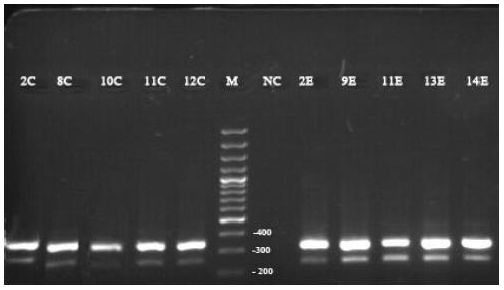
* **5-actin-forward:** 5-TCC TGC GGC ATC CAT GAA ACT-3
* **5-actin-reverse:** 5-ATC GTC CAC CGC AAA TGG TTC-3 which multiply a piece of 315 pairs of B-action gene. B-action is a house keeping gene and can be a good observer to investigate the whole process of mRNA delivery procedure. PCR processes include 35 repetitions from the 3 phases of 1: denaturation of 94 degree centigrade for 30 seconds 2: Annealing temperature of 58 degree centigrade for 30 seconds and 3: Extension temperature of 72 degree centigrade for 50 seconds.

To reach the best density of c DNA, different densities of c DNA were investigated and finally the best density for the final PCR was used. The research tests were repeated for at least three times. The investigation of the semi quantitative bands was done with the help of computer densitometer (Kodak, CT) and mRNA house keeping level was measured comparing to B-action gene house keeping.

**RESULTS**

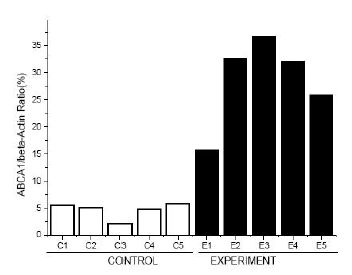
The ABCA1 expression was investigated by RT-PCR. The results clearly show that the ABCA1 expression increases in response to 6-weeks endurance training.

As you can see in Fig. 1, the B-action gene that is used as a controller of ABCA1 gene multiplication is expressed in all the samples. The ABCA1 expression in the  control group rats is very low and is clearly seen in the experimental group rats. After this phase, the semi quantitative investigation of the bands was done by the computer densitometer (Kodak, CT) and mRNA house keeping of ABCA1 was measured comparing to B-action gene house keeping.



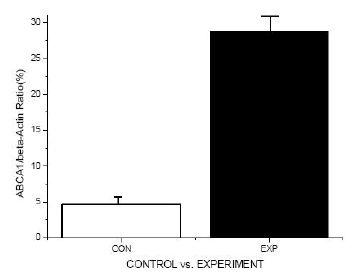
**Fig 1.** The picture of electrophorus jelly in ABCA1 and B-action genes of the control and experimental rats. 1C up to 5C control group, 1E up to 5 E experimental group, M marker and NC stand for negative control

As you can see in Fig. 2, the expression of ABCA1 gene in the experimental group is higher than the control one.



**Fig. 2.**mRNA house keeping percentage of ABCA1 gene comparing to B-action in each samples of experimental and control groups

As you can see in Fig. 3, the ABCA1 expression in the experimental group is generally higher than the control one.



**Fig. 3.** The ABCA1 expression in control and experimental groups

**DISCUSSION AND CONCLUSION**

The present research is undertaken to investigate the effect of Liver ABCA1 gene expression on the 6-week endurance training with moderate severity in the male rats.

A free activity life increases the risk of cardiovascular diseases while physical readiness and regular exercise may decrease the risk [42]. It seems that among the many useful effects of sport on the health, at least, a part of these benefits are related to the useful changes that happen in the blood lipoprotein profiles [27]. Most of the changes include Triglyceride, LDL, VLDL decrease and the HDL and its subsidiaries increase. [27,30,43]. It is shown that HDL shows its important role in the prevention of cardiovascular diseases through exerting excess cholesterol from peripheral cells and turning them to the liver in a procedure called Reverse Cholesterol  
Transit [44].

The ABCA1 transmitter is the main cholesterol and phospholipid exeter from the cell to the free-lipidated or minimally-lipidated Apo lipoprotein in order to form Pre Beta HDL. The scarce disease of tangier, the disease of fat metabolism disorder which 60 cases of it are reported in the world led to the recognition of the gene and ABCA1 protein function [45]. More studies among the animals free from ABCA1 gene confirmed the gene function in the Reverse Cholesterol Transfer and the formation of HDL mature particles [46]. On the other hand, some laboratories have tried to produce rats with excess ABCA1 expression [47-49]. It seems that the primary analysis of the rats confirms the useful increase of ABCA1 expression in the in vivo condition [46].

Although many studies have previously investigated the effect of different physical activities on the HDL [27] but only a few studies have investigated the HDL increase mechanisms. With regard to the importance of ABCA1 gene in the first phase of Reverse Cholesterol Transfer as well as its important role in the formation of mature HDL, the present research studied the expression the this gene by regular physical activity for the first time in the world. It is obvious from the results of the research that the ABCA1 gene is moderately expressed by regular endurance training. Therefore, a mechanism of increasing HDL through physical activity can increase the expression and consequently excess cholesterol exert from the cell by this transmitter.

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