



RESEARCH ARTICLE

Effect of Moderate Treadmill Exercise on Hepatic Lipid Metabolism in Rats

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Abstract

Several and complex factors cause accumulation of large amounts of body fat as well as a disparity between energy intake and output. Generally, any increase in bodyweight can be attributed to the elevation in daily food intake and the reduction in energy expenditure. Several functions could be achieved by moderate exercise including maintaining an optimum body weight and muscle mass, lowering abdominal fat and increasing lipid catabolism. However, the exact molecular mechanisms involved remain understudied. Our study was designed mainly to evaluate the influence of moderate treadmill exercise on body metabolism with special reference to hepatic lipid metabolism. Twenty adult male *Sprague Dawley* rats weighting 200 ± 20 gm were randomly assigned to either sedentary or exercised groups. The exercise protocol lasted for 20 mins/ 5 times / week along 4 weeks. Although no significant changes in body weight, insulin and corticosterone levels, there was a significant decrease in fasting blood glucose and serum leptin levels (81.06% and 75.49% respectively). The current exercise regime significantly increased serum high density lipoprotein (HDL-c) level (127.56%) and significantly decreased serum triacylglycerol (TAG), low density lipoprotein (LDL-c) and very low-density lipoprotein (VLDL-c) levels (75.50%, 62.83% and 74.48% respectively). Also, treadmill exercise significantly upregulated the hepatic expression of acetyl-CoA oxidase (ACO) and carnitine palmitoyl CoA transferase 1 (CPT1) (173% and 148% respectively) as well as significantly downregulated the hepatic acetyl-CoA carboxylase (ACC) (52%) but not fatty acid synthase (FAS) mRNA expression. Overall, these results suggest a beneficial effect of moderate treadmill exercise hepatic lipid metabolism.

Keywords: Treadmill exercise, ACC, FAS, ACO, CPT1

Introduction

Physical exercise is an effective method to promote health. Recently, an increased prevalence of obesity has been reported. Several undesirable health consequences are linked to that augmented adiposity making obesity a major health risk. Type 2 diabetes Mellitus (T2DM), cardiovascular complications, cancers, and even mortality have been found to be directly proportional to the obesity [1]. The increased body weight is ascribed to a reduction in daily expended energy [2]. Furthermore, high energy density

diet, sedentary lifestyle and eating disorders are considered major important risk factors for the development of obesity [3]. Taken together, such alterations lead to hypertrophy and hyperplasia of adipocytes, secretion of adipokines and inflammation [4]. A regular physical exercise and diet control are the main factors help to reduce weight [5] and improve lipid metabolism [6]. These effects are undoubtedly essential for maintaining a healthy lifestyle in both obese and non-obese individuals. The impact of moderate aerobic exercise in non-obese individuals remains

understudied; in particular for prevention of the development of adiposity and its related disorders. Furthermore, the proper exercise regime effect on bodily metabolism remains elusive.

Aerobic exercise, including treadmill training, is any exercise regime that improves cardiovascular fitness and boost oxygen uptake [7]. During which muscles depends mainly on aerobic metabolism and consume energy in the form of adenosine triphosphate (ATP) derived from amino acids, carbohydrates and fatty acids. In contrast, anaerobic exercise or resistance training intended to improve muscle mass and muscular strength occurs when oxygen does not adequate to supply the energy demands.

Overall, exercise represents a vital optional component of the daily energy expenditure [2], so that a proper regime can potentially affect energy balance. Physical activity has several beneficial health effects; not only in maintaining an optimal body weight and muscle mass, but also in reducing abdominal fat via lipid catabolism [8,9]. Regular aerobic exercise has a positive impact on the lipid profile [10].

The lipogenic enzymes, acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) are linked to fat accumulation [11]. Regular exercise in rodents has been reported to increase ACC phosphorylation and inactivation [12] and decrease FAS expression levels in fatty livers [13]. Both acetyl-CoA oxidase (ACO) and Carnitine palmitoyl CoA transferase 1 (CPT1) are essential for fatty acid oxidation [14] and conversion into energy. Following exercise, CPT1 expression was improved and an increased fatty acid oxidation was reported [15]. Appropriate exercise could potentially impact energy balance and influence the blood levels of leptin [16]. This study was mainly intended to evaluate a 4 weeks moderate treadmill exercise

regime effect on energy status especially hepatic lipid metabolism in male rats.

Materials and Methods

Experimental design

Twenty Adult male Sprague Dawley rats with initial mean body weight (200 ± 20) g were utilized in the study. Rats were obtained from laboratory animal unit of the Faculty of Veterinary Medicine, Zagazig University, with free access to water and chow. Animals care and use were performed following the rules of the Institutional Animal Care and Use Committee (IACUC) of Zagazig University (Approval no: ZU-IACUC/2/F/23/2019). After the acclimatization period, the experimental animals were randomly distributed into 2 equal groups (10 for each) as follow; Animals in group (1) were kept as sedentary rats as maintained under the same conditions as the experimental groups, but not subjected to any training, however those in group (2) were treadmill exercised rats for a daily 20 min for five days per week for one month. The current experiment took place in the animal facility of the Department of Physiology, Faculty of Veterinary Medicine, Zagazig University.

Aerobic exercise protocol

Rats were progressively and regularly adapted for training on the treadmill for ten days before the start of our experiment. The training duration lasted for 20 minutes for five days every week for a period of month [17] at the speed of (14 m/min) for moderate-intensity exercised groups, at 0° inclination [18]. Rats from the sedentary groups were left for similar period in stationary treadmill. The exercise protocol started daily at 9:00 am. Body weights were recorded once weekly before and during the experimental period.

Sampling

Animals were euthanized via cervical dislocation twenty-four hours after the last exercise session. The collected blood samples were left to clot then centrifuged for 15 min at 3000 rpm. Total serum was then separated and immediately stored at -20°C ready for subsequent biochemical analysis. Liver from

the two experimental groups were immediately removed. Approximately 50 mg of hepatic tissue from each rat were placed in liquid nitrogen, transferred to be stored at -80°C for subsequent gene expression analysis.

Biochemical and hormonal measurement:

Determination of serum glucose by oxidase method using Spectrum Diagnostics glucose kit [19]. Estimation of serum insulin, leptin and corticosterone levels were measured using commercially available rat enzyme-linked immunosorbent assay (ELISA) kits purchased from MyBioSource (San Diego, CA, USA). The direct enzymatic colorimetric liquid method used for determination of high-density lipoprotein (HDL-c) [20]. Serum low-density lipoprotein (LDL-c) and very low-density lipoprotein (VLDL-c) were calculated according to [21]. Evaluation of serum triacylglycerol (TAG) was carried out by enzymatic GPO-PAP- colorimetric method [22]. Cholesterol liquizyme enzymatic CHOD-PAP colorimetric method was used for determination of serum total cholesterol [23]. The biochemical parameters were measured by Semi-Auto Biochemical analyzer (SBA-733

plus) (SUNOSTIK medical technology) manufactured by Guangdong china.

Relative quantitative RT-PCR analysis

The protocols used were previously described in [24-26]. Briefly, Trizol reagent Invitrogen (ThermoFisher Scientific; Waltham, MA, United States) was used for total RNA extraction, a HiSenScript™ RH (-) cDNA Synthesis Kit (iNtRON Biotechnology Co., South Korea) was used for cDNA synthesis and a 5x HOT FIRE Pol EvaGreen qPCR Mix Plus (Solis BioDyne, Tartu, Estonia) was used for real time PCR according to manufacturer instruction. The real-time RT-PCR involved an initial denaturation at 95°C for 12 min, then 40 cycles of denaturation for 20 seconds at 95°C , annealing for 60 seconds at 60°C , and extension at 72°C for 60 seconds. The specific primers for the different genes of interest are presented in (Table 1) were synthesized by Sangon Biotech (Beijing, China). The target genes expression level was normalized to the housekeeping gene GAPDH. The relative gene expression fold changes were calculated based on the $2^{-\Delta\Delta\text{CT}}$ method [27].

Table1: Oligonucleotide primers sequences used for real time PCR.

Genes	Primers	Accession number
Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)	F: AAAGGGTCATCATCTCCGCC R: AGTGATGGCATGGACTGTGG	NM_017008.4
Fatty acid synthase (FAS)	F: GAGTATACAGCCACCGACCG R: AGTTGCACACCACAAGGTCA	NM_017332.1
Acetyl-CoA carboxylase (ACC)	F: AACAGTGTACAGCATCGCCA R: CATGCCGTAGTGGTTGAGGT	NM_022193.1
Carnitine Palmitoyl transferase 1A (Cpt1a)	F: GTACCAGCCCCGATGCCTTCAT R: TCTCTGTGCGACCCTCTCGGAA	NM_031559.2
Acyl-CoA Oxidase 1 (ACO1)	F:AAGAACTCCAGATAATTGGCACCTA R: TTTCCAAGCCTCGAAGATGAG	NM_017340.2

Statistical analysis:

The mean \pm standard error of the mean (SEM) was used for description of the data. Student's *t*-test using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA) was used to express the statistical significance. The values were statistically significant at $P < 0.05$.

Results**Effect of moderate exercise on body weight and hormonal level**

Moderate treadmill exercise did not induce significant changes in body weight compared to the sedentary rats (Figure 1A). Although no significant increase in serum insulin level (Figure 1B), a significant reduction in fasting blood glucose was shown (Figure 1C). A significant reduction in serum leptin level following moderate activity compared to control rats (Figure 1D). No significant alteration was noticed in the serum level of corticosterone between the two experimental groups (Figure 1E).

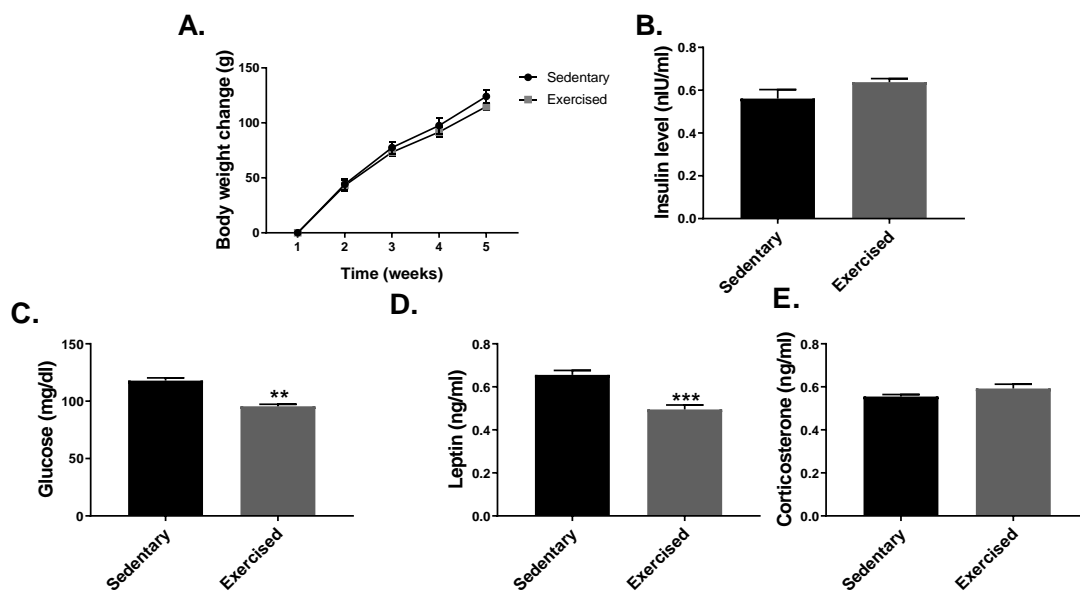


Figure1: Effect of moderate exercise on body weight and hormonal level: Data are expressed as means \pm SEM. n=10. ** $p < 0.01$, and * $p < 0.001$ versus sedentary group.**

Effect of moderate exercise on the lipid profile

Physical activity did not significantly change the serum level of TC compared to sedentary rat (Figure 2A). Moderate exercise significantly reduced serum levels of TAG, LDL-c and VLDL-c compared to control group (Figures, 2B, 2D, 2E). Treadmill training significantly increased the serum level of HDL-c compared to sedentary group (Figure 2C).

Effect of moderate exercise on hepatic gene expression

Treadmill training significantly downregulated the hepatic mRNA expression of ACC, but no significant changes were noticed in hepatic FAS expression levels between the two experimental groups (Figures, 3A, 3B). Moderate physical activity significantly upregulated hepatic mRNA expression of CPT1 and ACO compared to sedentary rats (Figures, 3C, 3D).

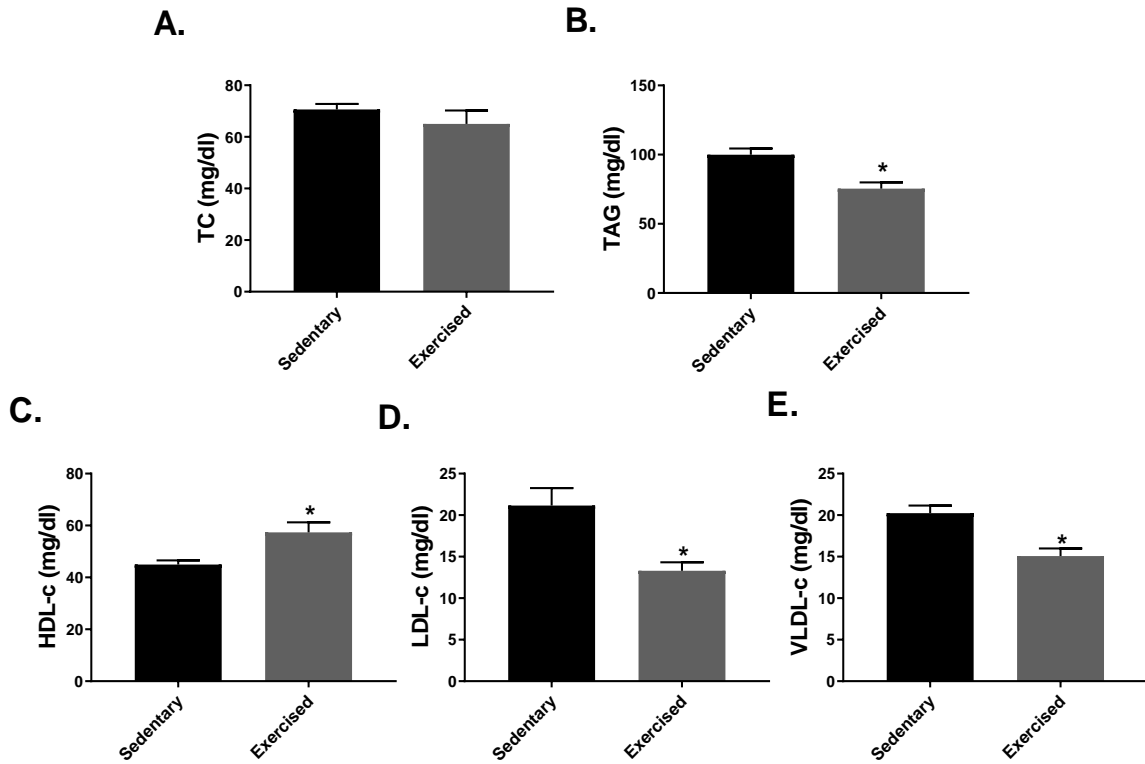


Figure2: Effect of moderate exercise on the lipid profile: Data are expressed as means \pm SEM. n=10. * p < 0.05 versus sedentary group. TC: Total cholesterol, TAG: Triacylglycerol, HDL-c: High density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol and VLDL-c: Very low-density lipoprotein cholesterol.

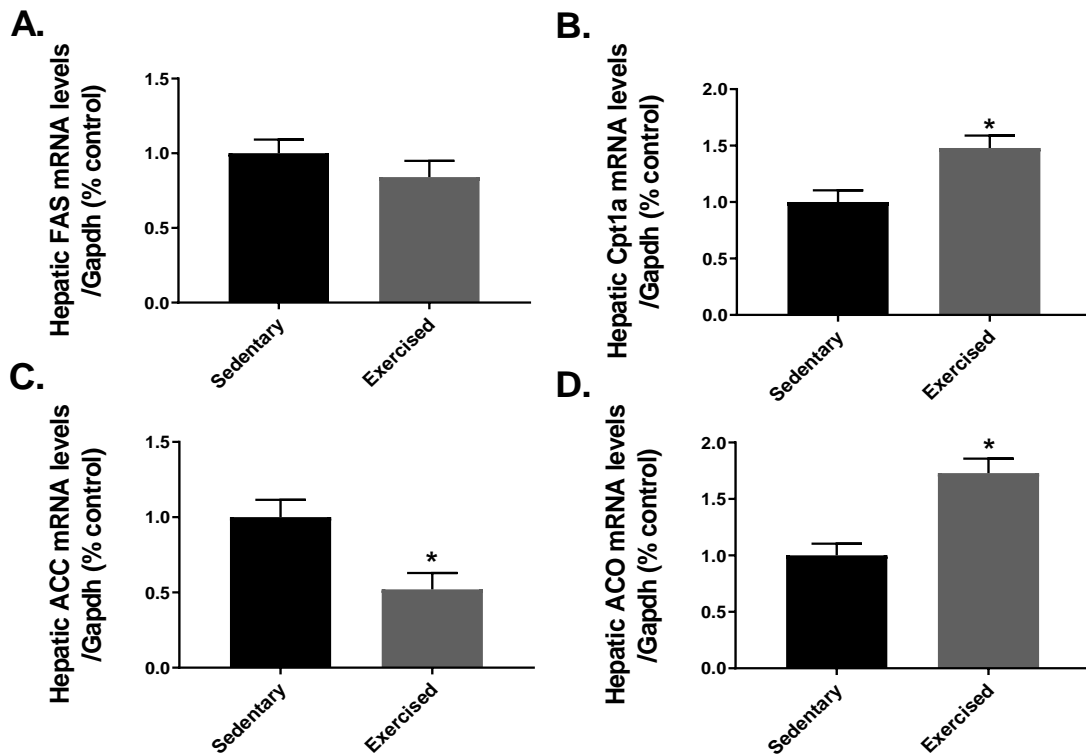


Figure3: Effect of moderate exercise on hepatic gene expression using real-time RT-PCR. Data are expressed as means \pm SEM. n=10. * p < 0.05 versus sedentary group.

Discussion

During the latest three decades, the obesity prevalence has expanded significantly. Proper exercise regime has various helpful health effects mainly via increasing the daily energy expenditure [2]. Yet, the complex mechanisms connecting exercise and metabolism remain not fully understood. The present study was aimed to evaluate the extent of effects of treadmill exercise on lipid metabolism both at whole organism or hepatic levels.

The exercised rats showed a non-significant change in final body weight when compared with sedentary rats. A decrease in weight occurring with exercise was reported by Borel *et al*, [28] who credited this reduction to lost fat mass with preserved lean mass. During prolonged moderate intensity exercise, a reduction in blood glucose was reported [29]. In consistent with Karacabey [30] who observed a decrease in insulin secretion of exercised group following 12 weeks of exercise. Our results showed a significant decrease in fasting blood glucose and serum leptin levels. The decline in insulin secretion in response to exercise is enhancing the peripheral utilization of glucose [31] due to improved whole-body insulin sensitivity [32]. Long term activity induces greater insulin sensitivity [33]. Either acute or chronic exercise stimulates adipose tissue via influencing its blood flow and fatty acids mobilization from the adipose tissue followed by the subsequent oxidation by the skeletal muscle [34]. These alterations in adipose tissue provoke the effects of exercise on ameliorating insulin sensitivity [35].

Regarding to lipid profile, our findings are consistent with Saritaş [8] who found a substantial increase in LDL-c level with significant diminishing in HDL-c level following 8-week aerobic training program. Moreover, 8-week [36] and 6-week [37] endurance training performed induced a critical increase in HDL-c with non-significant change in LDL-c.

The modifications of serum lipid profiles depend on several factors including diet of the subjects, weight status, beside to both duration and intensity of routine exercises [38]. The

physical activity to be beneficial and able to improve blood lipoprotein profiles should not exceed the anaerobic threshold [39]. If the exercises reached or exceed the anaerobic threshold, they have no helpful effect or even affect the blood lipoprotein profiles negatively [8].

The decrease in TAG in exercised group is consistent with Magkos *et al*, [40] who reported the remaining low levels of plasma TAG following an acute exercise bout for 24 h. In addition, rats exercised for 20 min treadmill exercise for five days per week for one month revealed a significant decrease in leptin comparing with sedentary animals in the present study. The serum concentrations of leptin change according to the intensity of exercise and the quantity of the energy consumed [41]. Olive *et al* in 2001 [42] showed that chronic exercise decreases leptin levels as a result of the diminishing in adipose tissue mass. The intense diminishing in leptin after a solitary bout of exercise may be an indicator to the body to increase energy intake to keep energy homeostasis inside a fine physiological range [43].

In the present study, corticosterone hormone revealed non-significant changes between all treated groups, which may be attributed to the progressive adaptation to treadmill exercise. Kraemer and Rogol [44] revealed that the progressive adaptation occurs, with a diminished adrenal reaction to the ACTH hormone released by exercise at the same relative intensity. Moreover, long-term exercise training can modulate oxidative stress that induced after acute exercise [45]. On the other hand, Luger *et al*, [46] observed that highly trained runners displayed trivial hypercortisolism at rest conditions while throughout the exercise; they showed slighter responses of the hypothalamus-hypophysis-adrenal axis. Treadmill exercise revealed a significant decrease in ACC but not in FAS gene expression and a significant increase in CPT1 and ACO gene expression comparing with sedentary rats' values which are in agreement with [47] who exhibited that hepatic fat accumulation is inhibited in exercise groups.

Furthermore, in rat (Otsuka Long Evans Tokushima Fatty (OLETF)) obesity model, the fat storage of liver declined [48] or prevented [49] following exercise training affiliated with reductions in ACC and FAS levels proving the correlation between exercise training impacts on intrahepatic lipid content and de novo lipogenesis action. The animals subjected to an intense exercise regimen combined with great dietary fat intake showed high CPT-1 α expression which is greater than that in animals exposed to only one of these circumstances [15]. After exercise, CPT-1 α expression is enhanced and related to expanded fatty acid oxidation [14].

Conclusion

In conclusion, the present study demonstrated that aerobic physical activity significantly influences fasting blood glucose level, improves lipid profile and regulates genes implicated in lipogenesis and β oxidation. Therefore, we can consider regular moderate aerobic exercise as a valid strategy to alleviate metabolic disorders and adiposity.

Conflict of Interest

The authors declare no conflicts of interest, financial or otherwise.

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الملخص العربي

تأثير ممارسة التمارين المعتدلة علي ابيض دهون الكبد في الفئران

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١- قسم الفسيولوجيا كلية الطب البيطري جامعه الزقازيق

٢- قسم الكيمياء الحيوية كلية الطب البيطري جامعه الزقازيق

تتسبب العديد من العوامل المعقدة في تراكم كميات كبيرة من الدهون في الجسم وكذلك التباين بين استهلاك وحرقة الطاقة. بشكل عام ويمكن أن تعزى أي زيادة في وزن الجسم إلى الارتفاع في الاستهلاك اليومي للغذاء وانخفاض حرق الطاقة. كما أن الممارسة المعتدلة للنشاط الرياضي لها فوائد مختلفة على الحالة الصحية، مثل الحفاظ على الوزن المثالي للجسم وكتلة العضلات، وخفض الدهون في البطن وزيادة هدم الدهون. ومع ذلك، فإن الآليات الجزيئية الدقيقة المعنية بدراسة هذه الجزئية تظل منقوصة. لذا فإن الهدف الرئيسي من هذه الدراسة هو تقييم تأثير الممارسة الرياضية المعتدلة على التمثيل الغذائي للجسم مع العناية بأبيض الدهون في الكبد. وقد أجريت هذه الدراسة باستخدام ٢٠ من ذكور الفئران البالغين التي تزن $200 \pm$ جرام، وزعت بشكل عشوائي إلى مجموعتين غير ممارستين للتمارين واخرى ممارسة للتمارين الرياضية. استمر بروتوكول التمرين لمدة ٢٠ دقيقة / ٥ مرات في الأسبوع / ٤ أسابيع. على الرغم من عدم ملاحظة أي تغييرات ملحوظة في وزن الجسم أو مستويات الأنسولين والكورتيكوستيرون، فقد لوحظ انخفاض كبير في معدل الجلوكوز الصائم في الدم. كما خفض نظام التمرين بشكل ملحوظ مستويات الدهون الثلاثية (TAG) والبروتين الدهني منخفض الكثافة (LDL-c) ومستويات البروتين الدهني منخفض الكثافة للغاية (VLDL-c) وكذلك زيادة البروتين الدهني عالي الكثافة في الدم (HDL-c). ممارسة الرياضة حسنت التعبير الكبدى لجينات لأسيثيل كو أ أو أكسيداز (ACO) و كاربونيتين بالميتويل ترانسفيريز (CPT1)، وكذلك قللت التعبير الجيني لأسيثيل كو أ كربوكسيلاز (ACC) ولكن ليس للفاتي اسيد سينسيز (FAS). عموماً، هذه النتائج تشير إلى وجود تأثير مفيد لممارسة الرياضة بصورة معتدلة خصوصاً أبيض الدهون في الكبد.