The Effect of Exercise on Paraoxonase-1 Activity and Lipid Profile in Obesity and Insulin Resistance Conditions

Hoseyn Fatolahi[1], Mohammad Ali Azarbayjani*[1], Maghsoud Peeri[1], Hasan Matin Homaee[1]

1. Department of Exercise Physiology, Central Tehran Branch, Islamic Azad University, Tehran, Iran.

***Correspondence:**
Mohammad Ali Azarbayjani, Department of Sport Physiology, Central Tehran Branch, Islamic Azad University, Tehran, Iran.
Email: ali.azarbayjani@gmail.com
Tel: (98) 912 317 2908

Received: 17 July 2017

Accepted: 07 September 2017

Published in October 2017

Abstract

In the absence of insulin, regular physical activity facilitates the glucose entry into the cell via affecting several signaling pathways. Moreover, regular exercise improves the lipid profile and increases the paraoxonase-1 (PON-1) activity. PON-1 interacts with High-density lipoprotein (HDL) and, in the presence of calcium, hydrolyzes free radicals, prevents low-density lipoprotein (LDL) oxidation, maintains homocysteine structure in the blood, and inhibits hemoglobin glycation. These factors explain one of the beneficial effects of regular exercise on prevention of cardiovascular diseases. In addition, there is a positive relationship between decreased PON-1 activity and the occurrence of cardiovascular diseases, renal failure, gastric cancer, dyslipidemia, insulin resistance, and even Alzheimer's disease. Therefore, this study was conducted to evaluate the effect of physical activity on the PON-1 activity and lipid profile. Regular physical activity increased HDL and PON-1 activity in patients with metabolic syndrome. Since PON-1 binds to HDL and increased HDL probably increases the PON-1 activity as well. This finding suggests that regular exercise decreases the effect of one bout exercise on PON-1 response. In addition, in order to improve metabolic syndromes, it is advised to perform aerobic exercise for 150 minutes per week with an intensity of 40-60% of the heart rate reserve (HRR). The exercises should be preferably performed in 3-5 sessions per week according to the intensity. Based on the disease progression, type of consumed drugs, and certain considerations in each group of patients, aerobic, resistance, and flexibility exercises can be performed by using large muscle groups in a continuous training mode. However, in dyslipidemia, continuous aerobic exercises are preferred.

Keywords: Physical activity, Diabetes, Paraoxonase, Lipid profile

Introduction

A sedentary lifestyle is associated with an increased risk of cardiovascular diseases and metabolic syndrome. On the other hand, regular physical activity is a protective factor against the occurrence and progression of these diseases and is associated with decreased blood pressure, maintenance of an appropriate body composition, lipid profile improvement,

and decreased type 2 diabetes mellitus signs (1). Moreover, regular physical exercise has positive effects on the metabolism of lipoproteins including decreasing plasma triglyceride (TG) and increasing the HDL-C concentration. Elevated HDL levels increase its antioxidant properties and protective effects against cardiovascular disease (2). HDL has anti-atherogenic and anti-LDL oxidation properties (3). The HDL antioxidant properties are related to the paraoxonase activity (aryl dialkyl phosphate) which can inhibit a number of phospholipids biological oxidizers (4). In addition, paraoxonase as an antioxidant and other antioxidants maintain the structure of homocysteine and prevent from hemoglobin destruction (5). Therefore, from a physiologic perspective and for research purposes it seems that measurement of the PON activity along with lipid profile is important.

Function and Biochemical Structure of PON enzyme

The current knowledge of PON indicates its anti-atherogenic properties as far as lack of PON gene expression is known risk factor of cardiovascular disease. The PON enzyme belongs to the family of calcium-dependent enzymes, including PON-1, PON-2, and PON-3 (6). Different PON enzymes are categorized according to their tissue distribution and expression, resulting in their physiologic differences. Most studies on PON-2 and PON-3 have mentioned their cell protective role as well as their role in cellular organelles like the mitochondrion (7) although the activity of one type of PON may be more prominent in different human or animal species. The PON-1 enzyme binds to HDL and has apo-protein AI and J (8). This enzyme is responsible for the antioxidant properties of HDL and PON-1 has a protective role against the progression of atherosclerosis (9,10). This finding was confirmed in rats which the expression of this gene was suppressed (4) or augmented (11). As that mentioned to the prevention of lipid oxidation, since oxidative stress is associated with progression of atherosclerosis, it seems that a balance between the sources of free radicals production and antioxidant activity, including increased PON-1 activity, plays a key role in decreasing cardiovascular diseases. Although PON is an important antioxidant, its measurement alone cannot show the antioxidant capacity of the body and other enzymatic, nutritional, and non-enzymatic antioxidants should also be evaluated.

The PON is a glycoprotein with 354 amino acids and a molecular weight of 44 kDa that can reversibly bind to organophosphorus compounds and hydrolyze them in the presence of 2 calcium ions (12). Since PON was first discovered during the breakdown of a pesticide known as paraoxon and its activity was studied in patients undergoing dialysis (13). The PON-1 is synthesized in the liver and binds to HDL unsaturated phospholipid chains (14). Changes in the size and volume of HDL markedly affect the antioxidant capacity of the PON-1, leading to controversies in the results of different studies (15). PON-1 also has catalytic properties like paraoxonase, arylesterase, diazoxonase, and lactonase activity (16). The PON-1 lactonase activity plays an important role in the maintenance of homocysteine (5,17). Simultaneous decreased activity of PON-1 and HDL and increased oxidized LDL are associated with many diseases (15,18). Apo protein-AI and J bind and execute paraoxonase (16,19).

It should be noted that PON-1 has different polymorphisms, which its genetic transcription can be affected by age, sex, physical activity, nutrition, and obesity and expressed on chromosome seven at different loci (19-21). A genetic change at position 191 results in the substitution of arginine (B) with glutamine (A), and substitution of methionine with leucine occurs at position 54 (22).

The Paraoxonase-1 activity and Diseases

Low PON-1 activity was reported in many diseases like obesity, diabetes, renal insufficiency, cancer, and metabolic syndrome (18,23). Its decreased activity was also showed

in cerebral vascular diseases, resulting in decreased blood flow to the brain and irreversible changes of the brain tissue, which is an important case of ischemic stroke (24).

The PON-1 activity is markedly decreased in diabetic postmenopausal women (25,26) and hyperlipidemia (2). However, some reports showed the activity of the enzyme is more important than the activity of its polymorphism especially in diabetes (27-29). The LDL is oxidized upon entering the cells via lipoxygenase and myeloperoxidase pathways (30) . The formation of this pre inflammatory compound stimulates the immune system and macrophages start digesting this compound, resulting in the production of foam cells and atheroma formation (30). This is the reason why PON-1 is helpful in treatment with statins (31). In some cases, the activity of PON-1 is independent of HDL and the enzymatic activity is low despite adequate HDL concentrations, which is probably more associated with the role of Apoproteins (29).

Atherosclerosis is more frequent in diabetic patients (32) probably due to the disturbed lipid profile and some other factors; paraoxonase-1 binds to Apo-AI and prevents LDL oxidation (33,34). In addition coronary artery disease (CAD) is the most common cause of death in diabetic patients (32). In this regard, some studies showed decreased salivary PON-1 activity in type 2 diabetic rats (35) although some other studies showed no differences between patients and controls (28). It is interesting that PON-1 activity decreases even in temporary conditions like pregnancy (36). However, lifestyle modification, even without changing the lipid profile and PON-1 concentration, increases their anti-inflammatory properties (37). Thyroid hormones disorders may decrease PON-1 activity on the metabolism of lipoproteins and mitochondrial activity (38). The oxidant condition and oxidative stress indexes were significantly worse in children with metabolic syndrome in comparison with control children, which could be the risk factor of many diseases in the future of their lives (39). In addition, there is a significant association between decreased expression of PON-1 gene and ovarian disorders in women (40). It is interesting that many studies have introduced hypertension, type 2 diabetes, obesity, dyslipidemia, decreased HDL, and oxidative stress as the risk factors of Alzheimer's disease (41). It also was reported that increased HDL and Apo-AI decrease the risk of Alzheimer's disease (42).

Lipid profile, PON-1 activity and herbal medicine

Many studies were done on the effects of medicinal plants, especially with exercise on diabetes and obesity (43,44). The increased activity of PON-1 following the consumption of herbal medicine is associated with vitamin E in their oil. Vitamin C, E, and polyphenols affect the activity of PON-1 (45,46). It is possible that some herbal medicines like cuminum cyminum L. affect blood glucose via increasing the insulin level (47). The foods containing flavonoids like pomegranate juice (48) and green tea (49) can affect PON-1 due to the number and position of their hydroxyl groups. It was previously reported that garlic (50) and hazelnut (51) decrease LDL and total cholesterol. Some herbal medicine like curcumin can regulate blood sugar, prevent liver damage and inflammation due to their antioxidant properties including PON-1 activity (52-55). It was recently reported that one of the most important activities of curcumin is preventing activation of NFkβ inflammatory pathways and increasing antioxidant defense (56,57). In this regard, there are confirmed reports on the antioxidant (58), anti-inflammatory and anti-cancer (59), hepatic protective (60), blood glucose lowering (53) and lipid lowering (54) effects of curcumin. The most interesting finding regarding turmeric and its effects on PON-1 and metabolic syndrome is prevention of hemoglobin glycation because free radicals disturb the cytochrome structure of heme-containing cells like hemoglobin compounds

(61). Turmeric prevents this injury due to its antioxidant properties and its effect on increasing PON-1 and therefore plays a role in controlling hemoglobin glycation. On the other hand, high levels of cholesterol change the hemoglobin structure. Therefore, increased antioxidant defense, especially PON-1, prevents both hemoglobin glycation and lipid oxidation. In addition, due to lactonase effects, PON-1 maintains the homocysteine structure and breakdown of homocysteine-thiolactone structure. As a result, PON-1 is an important cardiovascular protective factor and plays a significant role in controlling metabolic syndromes (5,17).

Effect of exercise on Lipid profile and PON-1 activity

Because extreme exercise in terms of oxidative stress (62) various aspects the effects of exercise on PON-1 activity were investigated. Theoretically, a single session of intense exercise results in the release of free radicals and increase oxidative pressure (63) while regular exercise acts as a protective and antioxidant factor. As will be mentioned regular exercise is also knows as a protective factor against the prevalence and progression of heart diseases. Free radicals increase during a single session of intense exercise and improve antioxidant mechanisms due to adaptation through signaling pathways. It should be noted that among factor affecting the lifestyle, physical activity is one of the regulators of the PON-1 activity. Previous findings have also shown that exercise affects PON-1 activity (62,64,65). However, there is no integrated information in this regard. The effect of physical activity on PON-1 activity may depend on the type and intensity of the exercise (62,64,65). The role on PON-1 exercise-related antioxidant mechanisms is not yet clear and therefore understanding the relationship between physical activity and PON-1 activity may have practical results.

Thomas et al (2002) reported that regular exercise had no effect on PON-1 activity while it increased following one session of intense aerobic exercise and returned to initial levels after 24 hours (66). Some other studies have reported similar effects in rats (67). These findings support the hypothesis that the oxidative stress due to intense physical activity increases lipid peroxidation, resulting in PON-1 activity and oxidant defense effort to prevention of lipid oxidation (68). Notice that separate bouts of intense exercise provide a great source of free radicals, oxidative stress, and lipid peroxidation condition (66). However, adaptation to intense exercise causes in response to single session of intense exercise increases the production of antioxidant agents and decreases lipid peroxidation (69), probably indicating PON-1 activation. It is interesting that this finding is not observed in untrained groups (70).

Possibly, after intense exercise lipid oxidation inactivates PON-1 through binding to free active sites and LDL oxidized lipids (71). These findings support the hypothesis that the oxidative stress resulting from physical activity in untrained people increases lipid peroxidation, which is in turn, associated with decreases PON-1 activity (68,72). In fact, oxidative stress somehow engages PON-1 in fighting free radical and lipid peroxidation. In confirmation of these findings, a significant increase in baseline activity of PON-1 is reported in soccer players in comparison with inactive groups (73). This finding suggests that regular exercise decreases the effect of one bout exercise on PON-1 response. Nevertheless, the mechanism of the effect of regular exercise on the changes of PON-1 activity in response to one bout intense exercise is unclear yet.

Moreover, regular exercise improves the antioxidant system (70,72,74), and decreases lipid peroxidation (72). However, the effects of regular exercise, even in trained people, are not fully protective against the effects of oxidative stress resulting from one bout intense exercise (74). The activity of antioxidants increases following regular exercise but increased oxidative stress resulting from intense physical activity is

probably more rapidly restored to baseline levels in trained people (74). Each session of physical activity results in the production of free radicals that trigger the production of antioxidants (74) (PON-1 for example). The factors that play a major role in the synthesis of PON-1 are affected by IL-6 and other inflammatory pathways, which is an acceptable explanation for decreased PON-1 activity and Intense physical activity increases oxidized phospholipids, which results in the secretion of pro-inflammatory cytokines like IL-6 and a decrease in PON-1 activity in rats (37,75). Little information is available on the effect of biological rhythms on PON-1 activity; however, the interaction is possible considering the effect of some hormones like estrogen on PON activity since estrogen decreases free radicals. It may be one of the reasons for the lower prevalence of cardiovascular diseases in premenopausal women versus men (25).

Roberts et al (2006) evaluated the effect of diet control and physical exercise on inflammatory and anti-inflammatory properties of HDL in men with cardiovascular risk factors (37). After three weeks, the anti-inflammatory effect of HDL-C was increased despite its low concentration. These findings suggest that rapid lifestyle changes improvement the effectiveness of HDL despite its low amount and changes its activity from pre-inflammatory to anti-inflammatory (37). It was reported that combination of aerobic exercise with 65% of VO_2max and niacin therapy increases the concentration and activity of PON-1 in metabolic syndrome patients (76). Moreover, it has been shown that aerobic exercise increases PON-1 in obese and people with metabolic syndrome (77,78). These findings have also been observed in cardiovascular rehabilitation groups (79). However, a study showed no marked changes in HDL and PON-1 levels even 6 months after aerobic exercise in obese women despite a considerable weight loss although the functional indexes of HDL and PON-1 improved (80). This finding suggests that a decrease in the HDL-C level is probably not a disease risk factor in obese diabetic or non-diabetic women if the lifestyle and diet are modified.

Nouno et al (2012) evaluated the relationship of PON-1 activity and lipid profile with cardiac diseases and the effect of flaxseed supplements on controlling dyslipidemia (81). Flaxseed has received a lot of attention in cardiac diseases because it is an important source of alpha-linolenic acid and fiber. Flaxseed supplementation in combination with regular exercise increased HDL and PON-1 significantly and decreased other cardiac markers like IL- 1β and TNF- α. Through flaxseed supplementation, regular physical activity improves the lipid profile and decreases the risk of cardiovascular diseases. The authors concluded that increased HDL and PON-1 resulting from the mutual effect of flaxseed supplement and physical exercise was protective against detrimental effects of acute myocardial ischemia (81).

Briefly, numerous studies have shown increased PON-1 activity following regular physical exercise. The most important point regarding the relationship between regular exercise and increased PON-1 activity is long-term adaptation and increased HDL in response to regular exercises. Since PON-1 binds to HDL and increased HDL probably increases the PON-1 activity, as well. However, no integrated information is available on changes in PON-1 activity in other types of exercise like a single session of intense exercise. Although adaptation with physical activity due to the impact of changes in lifestyle, environmental and genetic factors such as polymorphisms of PON-1 (65), But it has been shown that people who have had regularly exercise, have a less oxidative stress and more PON-1 activity in response to one bout intense exercise (64). Perhaps some of the adaptations with training that reduce the need to insulin and improve physical fitness in patients with type-1 diabetes (82). It has also been reported that improve the serum lipid profile in response to concurrent exercise

(endurance & resistance exercise training simultaneously), in healthy untrained participants (83) and people with diabetes type-1 (82) Respectively. It is reported that most important of these changes is an increase in HDL in patients with type-2 diabetes (78). As mentioned on the role of medicinal plants some researchers have reported that aerobic exercise is combined with use of herbal medicines will play an important role in improvement of lipid profile (44,81). In addition, it has been shown that exercise with light and moderate intensity improved the lipid profile in obese and overweight groups (84).

Physical activity and Signaling Pathways affecting glucose uptake

The pathogenesis of metabolic syndromes is lack of blood glucose regulation and increased oxidative stress in these patients. Since the liver has a prominent role in the production of blood glucose, increased blood glucose disturbs oxidation-reduction (redox) reactions in hepatocytes, leading to the production of free radicals. Therefore, blood glucose control alone does not prevent secondary complications. Even blood glucose regulating drugs have side effects and have no role in preventing secondary complications. However, attention has been paid to physical activity due to its insulin-like effects. Insulin is a known factor in glucose uptake by cells but its secretion stops during exercise. On the other hand, insulin is necessary for glucose to enter muscle cells. Interestingly, several folds increase glucose uptake during exercise. Therefore, it can be concluded that factors other than insulin are involved in glucose entry into the cells. Care must be taken that physical activity and insulin have synergistic effects and markedly decrease blood glucose. It has been well demonstrated that muscular contraction has insulin-like effects through known and unknown pathways. However, up-regulation of insulin receptors occurs after and not during physical activity, which is desirable and remains stable in the body for hours after the exercise, and lowers the need for drugs (85,86). On the other hand, some studies have shown that increase TNF-α following muscular injury in intense exercises containing eccentric contraction results in the blockade of signaling pathways (86) and may be a reason for fatigue. Apart from known hormonal pathways that actually augment or inhibit cellular and molecular pathways, the most important signaling pathway of insulin stimulation is formed in response to increased metabolic needs that activates a complex of proteins, resulting in GLUT-4 translocation and even an increase in its gene expression even after the exercise (87). One of the most important advantages of exercise in diabetic patients is increasing the number and sensitivity of insulin receptors after physical activity. Following a training session, the glycogen in the muscle is depleted, resulting in an increase in glycogenesis enzymes. In fact, glycogen depletion is the main factor for glucose entry into the cell because if all conditions are met but the cell does not need glucose, it will not enter the cell (43,87).

Evaluations have shown that increased calcium ion during muscular contractions in physical activity play an important role in glucose entry during exercise. Calcium plays its role though activation of protein kinase C (PKC) and Calcium-calmodulin (CaMK) second messenger mechanism (88). Another mechanism is the activity of phosphatidylinositol kinase-3 (PI3K) enzyme that is more controlled by insulin than physical activity. The absence of insulin or any failure in its receptors results in the inhibition of this enzyme and inhibition of glucose entry into the cell. In the breakdown of membrane phospholipids as a second messenger mechanism, PIP2 breaks down to IP3 and DAG. The IP3 pathway results in calcium release with known mechanisms while the DAG pathway results in the production of PKC and prostaglandins, especially E2 (89). Some studies have shown that inhibition of PKC enzyme disturbs the process of glucose transpiration. This mechanism is one of the

mechanisms of the effect of contraction and more contraction enhances glucose entry.

In addition, the NO activity is increased during exercise. It has been shown that inhibition of NO production and adenosine disturbs glucose entry (90) which is probably due to affecting the blood flow to the muscle. On the other hand, NO activates the signaling pathways of glucose entry into the cell, including (mitogen activated protein kinase) MAPK, JNK, ERK, and P38 (91,92). In addition to the above pathways, it has been mentioned that during exercise, due to ATP consumption and decreased ATP to ADP ratio, adenosine monophosphate-activated protein kinase (AMPK), which works under the influence of the ATP to ADP ratio, enhances glucose uptake (93).

Conclusion and exercise prescription

Although many studies have evaluated the effect of physical exercise on PON-1 activity is patients and healthy individuals, it is hard to reach an integrated conclusion because PON-1 activity is regulated by many factors and exercise is one of them. The possible reasons were discussed in the previous section.

Attention should be paid to the FITT-VP components of exercise prescription including Frequency, Intensity, Time (duration), Type (mode), Volume (quantity), and Progression proposed by American College of Sports Medicine (ACSM) (94-96). Therefore, it should be noted that before exercise prescription, the person should be evaluated for physical capabilities and biochemical indexes. There is need for exercise testing beyond the PAR-Q questionnaire, medical history, and biochemical tests before exercises. However, people with cardiovascular diseases should undergo graded exercise tests and electrocardiography before exercise although they do not eliminate the risk of accidents (94-96).

According to the ACSM's guidelines, aerobic, resistance, and flexibility exercises can be performed in diabetic patients with a frequency of 3-5 sessions per week and intensity of 40-60% of HRR or a score of 11-13 in the Borg Rating of Perceived Exertion Scale (6 to 20 points). These activities should be performed for 150 minutes per week in separate sessions and should preferably increase to 300 minutes. These activities should be performed according to the person's preference using large muscle groups in a rhythmic and continuous mode. Some studies have shown that a combination of aerobic and resistance training has better results (82). The person should not be inactive for two consecutive days. Moreover, attention should be paid to the goal of exercise in these people, i.e. cardiovascular preparedness, weight loss, etc. blood glucose should be monitored regularly to prevent hypoglycemia. These patients should use special ointments and socks for a better hand and foot care (82). It should be borne in mind that glucose metabolism defects may result in hyperglycemia with ketosis (97). Moreover, dehydration following polyuria can be an effective factor in lack of temperature regulation and electrolyte balance. Diabetic patients with retinopathy should do very light exercise to prevent excessive increase in blood pressure, retinal injury, and severe hemorrhage (97). Improved glucose tolerance and increased insulin sensitivity are observed in patients with type II diabetes and the need for insulin decreases in type 1 diabetic patients (82). A diabetic patient with neuropathy or ocular laser surgery should avoid from resistance training (97). Hypoglycemia is the most important complication in these patients which is more often seen in patients receiving insulin or other glucose lowering drugs (94-96).

Abnormal concentrations of lipids and lipoproteins are known as dyslipidemia. Dyslipidemia occur when the LDL concentration increases or the HDL concentration decreases (94-96). In summary, aerobic training is more recommended in lipid disorders (84). The ACSM also recommends aerobic training for patients with lipid disorders; the person should do aerobic

training 5 days a week at 40-70% of HRR. It is recommended to exercise 30-60 minutes per session. These people should do aerobic training 250 minutes per week to both decrease the fat mass and change the lipid profile. If the person has, other disorders like diabetes or hypertension besides lipid disorders, its certain considerations should be regarded. Some lipid lowering agents as statins cause muscle weakness, severe muscle soreness, or myalgia, which require exercise modification.

References

1. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation. 2007;116(9):1081-93.
2. Leaf DA. The effect of physical exercise on reverse cholesterol transport. Metabolism: clinical and experimental. 2003;52(8):950-7.
3. Parthasarathy S, Barnett J, Fong LG. High-density lipoprotein inhibits the oxidative modification of low-density lipoprotein. Biochimica et biophysica acta. 1990;1044(2):275-83.
4. Shih DM, Xia YR, Wang XP, Miller E, Castellani LW, Subbanagounder G, et al. Combined serum paraoxonase knockout/apolipoprotein E knockout mice exhibit increased lipoprotein oxidation and atherosclerosis. The Journal of biological chemistry. 2000;275(23):17527-35.
5. Jakubowski H. The role of paraoxonase 1 in the detoxification of homocysteine thiolactone. Advances in experimental medicine and biology. 2010;660:113-27.
6. Primo-Parmo SL, Sorenson RC, Teiber J, La Du BN. The human serum paraoxonase/arylesterase gene (PON1) is one member of a multigene family. Genomics. 1996;33(3):498-507.
7. Devarajan A, Bourquard N, Hama S, Navab M, Grijalva VR, Morvardi S, et al. Paraoxonase 2 deficiency alters mitochondrial function and exacerbates the development of atherosclerosis. Antioxidants & redox signaling. 2011;14(3):341-51.
8. Goswami B, Rajappa M, Mallika V, Kumar S, Shukla DK. Apo-B/apo-AI ratio: a better discriminator of coronary artery disease risk than other conventional lipid ratios in Indian patients with acute myocardial infarction. Acta cardiologica. 2008;63(6):749-55.
9. Mackness MI, Arrol S, Abbott C, Durrington PN. Protection of low-density lipoprotein against oxidative modification by high-density lipoprotein associated paraoxonase. Atherosclerosis. 1993;104(1-2):129-35.
10. Mackness MI, Arrol S, Durrington PN. Paraoxonase prevents accumulation of lipoperoxides in low-density lipoprotein. FEBS letters. 1991;286(1-2):152-4.
11. Tward A, Xia YR, Wang XP, Shi YS, Park C, Castellani LW, et al. Decreased atherosclerotic lesion formation in human serum paraoxonase transgenic mice. Circulation. 2002;106(4):484-90.
12. Durrington PN, Mackness B, Mackness MI. Paraoxonase and atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology. 2001;21(4):473-80.
13. Juretic D, Tadijanovic M, Rekic B, Simeon-Rudolf V, Reiner E, Baricic M. Serum paraoxonase activities in hemodialyzed uremic patients: cohort study. Croatian medical journal. 2001;42(2):146-50.
14. Oda MN, Bielicki JK, Ho TT, Berger T, Rubin EM, Forte TM. Paraoxonase 1 overexpression in mice and its effect on high-density lipoproteins. Biochemical and biophysical research communications. 2002;290(3):921-7.
15. Li HL, Liu DP, Liang CC. Paraoxonase gene polymorphisms, oxidative stress, and diseases. Journal of molecular medicine. 2003;81(12):766-79.
16. Ferre N, Tous M, Paul A, Zamora A, Vendrell JJ, Bardaji A, et al. Paraoxonase Gln-Arg(192) and Leu-Met(55) gene polymorphisms and enzyme activity in a population with a low rate of coronary heart disease. Clinical biochemistry. 2002;35(3):197-203.
17. Billecke S, Draganov D, Counsell R, Stetson P, Watson C, Hsu C, et al. Human serum paraoxonase (PON1) isozymes Q and R hydrolyze lactones and cyclic carbonate esters. Drug metabolism and disposition: the biological fate of chemicals. 2000;28(11):1335-42.
18. Camps J, Marsillach J, Joven J. The paraoxonases: role in human diseases and methodological difficulties in measurement. Critical reviews in clinical laboratory sciences. 2009;46(2):83-106.
19. Ferre N, Camps J, Fernandez-Ballart J, Arija V, Murphy MM, Ceruelo S, et al. Regulation of serum paraoxonase activity by genetic, nutritional, and lifestyle factors in the general population. Clinical chemistry. 2003;49(9):1491-7.
20. Sutherland WH, Walker RJ, de Jong SA, van Rij AM, Phillips V, Walker HL. Reduced postprandial serum paraoxonase activity after a meal rich in used

cooking fat. Arteriosclerosis, thrombosis, and vascular biology. 1999;19(5):1340-7.
21. Zama T, Murata M, Matsubara Y, Kawano K, Aoki N, Yoshino H, et al. A 192Arg variant of the human paraoxonase (HUMPONA) gene polymorphism is associated with an increased risk for coronary artery disease in the Japanese. Arteriosclerosis, thrombosis, and vascular biology. 1997;17(12):3565-9.
22. Adkins S, Gan KN, Mody M, La Du BN. Molecular basis for the polymorphic forms of human serum paraoxonase/arylesterase: glutamine or arginine at position 191, for the respective A or B allozymes. American journal of human genetics. 1993;52(3):598-608.
23. Camps J, Marsillach J, Joven J. Measurement of serum paraoxonase-1 activity in the evaluation of liver function. World journal of gastroenterology. 2009;15(16):1929-33.
24. Kostapanos MS, Christogiannis LG, Bika E, Bairaktari ET, Goudevenos JA, Elisaf MS, et al. Apolipoprotein B-to-A1 ratio as a predictor of acute ischemic nonembolic stroke in elderly subjects. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2010;19(6):497-502.
25. Sutherland WH, Manning PJ, de Jong SA, Allum AR, Jones SD, Williams SM. Hormone-replacement therapy increases serum paraoxonase arylesterase activity in diabetic postmenopausal women. Metabolism: clinical and experimental. 2001;50(3):319-24.
26. Teiber JF, Billecke SS, La Du BN, Draganov DI. Estrogen esters as substrates for human paraoxonases. Archives of biochemistry and biophysics. 2007;461(1):24-9.
27. Mackness B, Durrington PN, Abuashia B, Boulton AJ, Mackness MI. Low paraoxonase activity in type II diabetes mellitus complicated by retinopathy. Clinical science. 2000;98(3):355-63.
28. Mackness B, Durrington PN, Boulton AJ, Hine D, Mackness MI. Serum paraoxonase activity in patients with type 1 diabetes compared to healthy controls. European journal of clinical investigation. 2002;32(4):259-64.
29. Mackness MI, Harty D, Bhatnagar D, Winocour PH, Arrol S, Ishola M, et al. Serum paraoxonase activity in familial hypercholesterolaemia and insulin-dependent diabetes mellitus. Atherosclerosis. 1991;86(2-3):193-9.
30. van Himbergen TM, van Tits LJ, Roest M, Stalenhoef AF. The story of PON1: how an organophosphate-hydrolysing enzyme is becoming a player in cardiovascular medicine. The Netherlands journal of medicine. 2006;64(2):34-8.
31. Gouedard C, Koum-Besson N, Barouki R, Morel Y. Opposite regulation of the human paraoxonase-1 gene PON-1 by fenofibrate and statins. Molecular pharmacology. 2003;63(4):945-56.
32. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. The New England journal of medicine. 1998;339(4):229-34.
33. Navab M, Hama SY, Anantharamaiah GM, Hassan K, Hough GP, Watson AD, et al. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: steps 2 and 3. Journal of lipid research. 2000;41(9):1495-508.
34. Navab M, Hama SY, Cooke CJ, Anantharamaiah GM, Chaddha M, Jin L, et al. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: step 1. Journal of lipid research. 2000;41(9):1481-94.
35. Ghaffari T, Nouri M, Irannejad E, Rashidi MR. Effect of vitamin e and selenium supplement on paraoxonase-1 activity, oxidized low density lipoprotein and antioxidant defense in diabetic rats. BioImpacts : BI. 2011;1(2):121-8.
36. Weitman SD, Vodicnik MJ, Lech JJ. Influence of pregnancy on parathion toxicity and disposition. Toxicology and applied pharmacology. 1983;71(2):215-24.
37. Roberts CK, Ng C, Hama S, Eliseo AJ, Barnard RJ. Effect of a short-term diet and exercise intervention on inflammatory/anti-inflammatory properties of HDL in overweight/obese men with cardiovascular risk factors. Journal of applied physiology. 2006;101(6):1727-32.
38. Erem C, Deger O, Bostan M, Orem A, Sonmez M, Ulusoy S, et al. Plasma lipoprotein (a) concentrations in hypothyroid, euthyroid and hyperthyroid subjects. Acta cardiologica. 1999;54(2):77-81.
39. Eren E, Abuhandan M, Solmaz A, Taskin A. Serum paraoxonase/arylesterase activity and oxidative stress status in children with metabolic syndrome. Journal of clinical research in pediatric endocrinology. 2014;6(3):163-8.
40. Wang Y, Liu H, Fan P, Bai H, Zhang J, Zhang F. Evidence for association between paraoxonase 1 gene polymorphisms and polycystic ovarian syndrome in southwest Chinese women. European journal of endocrinology. 2012;166(5):877-85.
41. Vagelatos NT, Eslick GD. Type 2 diabetes as a risk factor for Alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. Epidemiologic reviews. 2013;35:152-60.
42. Reitz C, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer

disease. Archives of neurology. 2010;67(12):1491-7.
43. Dehghan F, Hajiaghaalipour F, Yusof A, Muniandy S, Hosseini SA, Heydari S, et al. Saffron with resistance exercise improves diabetic parameters through the GLUT4/AMPK pathway in-vitro and in-vivo. Scientific reports. 2016;6:25139.
44. Khosravani M, Azarbayjani MA, Abolmaesoomi M, Yusof A, Zainal Abidin N, Rahimi E, et al. Ginger extract and aerobic training reduces lipid profile in high-fat fed diet rats. European review for medical and pharmacological sciences. 2016;20(8):1617-22.
45. Gouedard C, Barouki R, Morel Y. Dietary polyphenols increase paraoxonase 1 gene expression by an aryl hydrocarbon receptor-dependent mechanism. Molecular and cellular biology. 2004;24(12):5209-22.
46. Jarvik GP, Tsai NT, McKinstry LA, Wani R, Brophy VH, Richter RJ, et al. Vitamin C and E intake is associated with increased paraoxonase activity. Arteriosclerosis, thrombosis, and vascular biology. 2002;22(8):1329-33.
47. Dhandapani S, Subramanian VR, Rajagopal S, Namasivayam N. Hypolipidemic effect of Cuminum cyminum L. on alloxan-induced diabetic rats. Pharmacological research. 2002;46(3):251-5.
48. Boesch-Saadatmandi C, Egert S, Schrader C, Coumoul X, Barouki R, Muller MJ, et al. Effect of quercetin on paraoxonase 1 activity--studies in cultured cells, mice and humans. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society. 2010;61(1):99-105.
49. Rosenblat M, Volkova N, Coleman R, Almagor Y, Aviram M. Antiatherogenicity of extra virgin olive oil and its enrichment with green tea polyphenols in the atherosclerotic apolipoprotein-E-deficient mice: enhanced macrophage cholesterol efflux. The Journal of nutritional biochemistry. 2008;19(8):514-23.
50. Durak I, Kavutcu M, Aytac B, Avci A, Devrim E, Ozbek H, et al. Effects of garlic extract consumption on blood lipid and oxidant/antioxidant parameters in humans with high blood cholesterol. The Journal of nutritional biochemistry. 2004;15(6):373-7.
51. Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Annals of internal medicine. 2006;145(1):1-11.
52. Araujo CC, Leon LL. Biological activities of Curcuma longa L. Memorias do Instituto Oswaldo Cruz. 2001;96(5):723-8.
53. Arun N, Nalini N. Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. Plant foods for human nutrition. 2002;57(1):41-52.
54. Babu PS, Srinivasan K. Hypolipidemic action of curcumin, the active principle of turmeric (Curcuma longa) in streptozotocin induced diabetic rats. Molecular and cellular biochemistry. 1997;166(1-2):169-75.
55. Mahesh T, Balasubashini MS, Menon VP. Effect of photo-irradiated curcumin treatment against oxidative stress in streptozotocin-induced diabetic rats. Journal of medicinal food. 2005;8(2):251-5.
56. Marquardt JU, Gomez-Quiroz L, Arreguin Camacho LO, Pinna F, Lee YH, Kitade M, et al. Curcumin effectively inhibits oncogenic NF-kappaB signaling and restrains stemness features in liver cancer. Journal of hepatology. 2015;63(3):661-9.
57. Olivera A, Moore TW, Hu F, Brown AP, Sun A, Liotta DC, et al. Inhibition of the NF-kappaB signaling pathway by the curcumin analog, 3,5-Bis(2-pyridinylmethylidene)-4-piperidone (EF31): anti-inflammatory and anti-cancer properties. International immunopharmacology. 2012;12(2):368-77.
58. Sreejayan, Rao MN. Nitric oxide scavenging by curcuminoids. The Journal of pharmacy and pharmacology. 1997;49(1):105-7.
59. Brouet I, Ohshima H. Curcumin, an anti-tumour promoter and anti-inflammatory agent, inhibits induction of nitric oxide synthase in activated macrophages. Biochemical and biophysical research communications. 1995;206(2):533-40.
60. Kiso Y, Suzuki Y, Watanabe N, Oshima Y, Hikino H. Antihepatotoxic principles of Curcuma longa rhizomes. Planta medica. 1983;49(3):185-7.
61. Cross AR, Jones OT. Enzymic mechanisms of superoxide production. Biochimica et biophysica acta. 1991;1057(3):281-98.
62. Otocka-Kmiecik A, Lewandowski M, Stolarek R, Szkudlarek U, Nowak D, Orlowska-Majdak M. Effect of single bout of maximal exercise on plasma antioxidant status and paraoxonase activity in young sportsmen. Redox report : communications in free radical research. 2010;15(6):275-81.
63. Morales-Alamo D, Calbet JA. Free radicals and sprint exercise in humans. Free radical research. 2014;48(1):30-42.
64. Otocka-Kmiecik A, Lewandowski M, Szkudlarek U, Nowak D, Orlowska-Majdak M. Aerobic training modulates the effects of exercise-induced oxidative stress on PON1 activity: a preliminary study. TheScientificWorldJournal. 2014;2014:230271.
65. Otocka-Kmiecik A, Orlowska-Majdak M. The role of genetic (PON1 polymorphism) and environmental factors, especially physical activity, in antioxidant function of paraoxonase. Postepy higieny i medycyny doswiadczalnej. 2009;63:668-77.

66. Tomas M, Elosua R, Senti M, Molina L, Vila J, Anglada R, et al. Paraoxonase1-192 polymorphism modulates the effects of regular and acute exercise on paraoxonase1 activity. Journal of lipid research. 2002;43(5):713-20.
67. Pawlowska D, Moniuszko-Jakoniuk J, Soltys M. The effect of chronic physical exercise on the activity of hydrolytic enzymes in acute poisoning with parathion-methyl in rats. Polish journal of pharmacology and pharmacy. 1985;37(5):639-46.
68. Aviram M, Rosenblat M, Billecke S, Erogul J, Sorenson R, Bisgaier CL, et al. Human serum paraoxonase (PON 1) is inactivated by oxidized low density lipoprotein and preserved by antioxidants. Free radical biology & medicine. 1999;26(7-8):892-904.
69. Somani SM, Rybak LP. Comparative effects of exercise training on transcription of antioxidant enzyme and the activity in old rat heart. Indian journal of physiology and pharmacology. 1996;40(3):205-12.
70. Alessio HM, Goldfarb AH. Lipid peroxidation and scavenger enzymes during exercise: adaptive response to training. Journal of applied physiology. 1988;64(4):1333-6.
71. Aviram M, Billecke S, Sorenson R, Bisgaier C, Newton R, Rosenblat M, et al. Paraoxonase active site required for protection against LDL oxidation involves its free sulfhydryl group and is different from that required for its arylesterase/paraoxonase activities: selective action of human paraoxonase allozymes Q and R. Arteriosclerosis, thrombosis, and vascular biology. 1998;18(10):1617-24.
72. Clarkson PM. Antioxidants and physical performance. Critical reviews in food science and nutrition. 1995;35(1-2):131-41.
73. Brites FD, Evelson PA, Christiansen MG, Nicol MF, Basilico MJ, Wikinski RW, et al. Soccer players under regular training show oxidative stress but an improved plasma antioxidant status. Clinical science. 1999;96(4):381-5.
74. Sen CK. Oxidants and antioxidants in exercise. Journal of applied physiology. 1995;79(3):675-86.
75. Van Lenten BJ, Wagner AC, Navab M, Fogelman AM. Oxidized phospholipids induce changes in hepatic paraoxonase and ApoJ but not monocyte chemoattractant protein-1 via interleukin-6. The Journal of biological chemistry. 2001;276(3):1923-9.
76. Taylor JK, Plaisance EP, Mahurin AJ, Mestek ML, Moncada-Jimenez J, Grandjean PW. Paraoxonase responses to exercise and niacin therapy in men with metabolic syndrome. Redox report : communications in free radical research. 2015;20(1):42-8.
77. Casella-Filho A, Chagas AC, Maranhao RC, Trombetta IC, Cesena FH, Silva VM, et al. Effect of exercise training on plasma levels and functional properties of high-density lipoprotein cholesterol in the metabolic syndrome. The American journal of cardiology. 2011;107(8):1168-72.
78. Iborra RT, Ribeiro IC, Neves MQ, Charf AM, Lottenberg SA, Negrao CE, et al. Aerobic exercise training improves the role of high-density lipoprotein antioxidant and reduces plasma lipid peroxidation in type 2 diabetes mellitus. Scandinavian journal of medicine & science in sports. 2008;18(6):742-50.
79. Goldhammer E, Ben-Sira D, Zaid G, Biniamini Y, Maor I, Lanir A, et al. Paraoxonase activity following exercise-based cardiac rehabilitation program. Journal of cardiopulmonary rehabilitation and prevention. 2007;27(3):151-4.
80. Aicher BO, Haser EK, Freeman LA, Carnie AV, Stonik JA, Wang X, et al. Diet-induced weight loss in overweight or obese women and changes in high-density lipoprotein levels and function. Obesity. 2012;20(10):2057-62.
81. Nounou HA, Deif MM, Shalaby MA. Effect of flaxseed supplementation and exercise training on lipid profile, oxidative stress and inflammation in rats with myocardial ischemia. Lipids in health and disease. 2012;11:129.
82. D'Hooge R, Hellinckx T, Van Laethem C, Stegen S, De Schepper J, Van Aken S, et al. Influence of combined aerobic and resistance training on metabolic control, cardiovascular fitness and quality of life in adolescents with type 1 diabetes: a randomized controlled trial. Clinical rehabilitation. 2011;25(4):349-59.
83. Ghahramanloo E, Midgley AW, Bentley DJ. The effect of concurrent training on blood lipid profile and anthropometrical characteristics of previously untrained men. Journal of physical activity & health. 2009;6(6):760-6.
84. Marandi SM, Abadi NG, Esfarjani F, Mojtahedi H, Ghasemi G. Effects of intensity of aerobics on body composition and blood lipid profile in obese/overweight females. International journal of preventive medicine. 2013;4(Suppl 1):S118-25.
85. Hayashi T, Wojtaszewski JF, Goodyear LJ. Exercise regulation of glucose transport in skeletal muscle. The American journal of physiology. 1997;273(6 Pt 1):E1039-51.
86. Kirwan JP, del Aguila LF. Insulin signalling, exercise and cellular integrity. Biochemical Society transactions. 2003;31(Pt 6):1281-5.
87. Kuo CH, Browning KS, Ivy JL. Regulation of GLUT4 protein expression and glycogen storage after prolonged exercise. Acta physiologica Scandinavica. 1999;165(2):193-201.
88. Wright DC, Hucker KA, Holloszy JO, Han DH. Ca2+ and AMPK both mediate stimulation of glucose transport by muscle contractions. Diabetes. 2004;53(2):330-5.

89. Ihlemann J, Ploug T, Hellsten Y, Galbo H. Effect of tension on contraction-induced glucose transport in rat skeletal muscle. The American journal of physiology. 1999;277(2 Pt 1):E208-14.
90. Bradley SJ, Kingwell BA, McConell GK. Nitric oxide synthase inhibition reduces leg glucose uptake but not blood flow during dynamic exercise in humans. Diabetes. 1999;48(9):1815-21.
91. Chen HC, Bandyopadhyay G, Sajan MP, Kanoh Y, Standaert M, Farese RV, Jr., et al. Activation of the ERK pathway and atypical protein kinase C isoforms in exercise- and aminoimidazole-4-carboxamide-1-beta-D-riboside (AICAR)-stimulated glucose transport. The Journal of biological chemistry. 2002;277(26):23554-62.
92. Somwar R, Perreault M, Kapur S, Taha C, Sweeney G, Ramlal T, et al. Activation of p38 mitogen-activated protein kinase alpha and beta by insulin and contraction in rat skeletal muscle: potential role in the stimulation of glucose transport. Diabetes. 2000;49(11):1794-800.
93. Musi N, Yu H, Goodyear LJ. AMP-activated protein kinase regulation and action in skeletal muscle during exercise. Biochemical Society transactions. 2003;31(Pt 1):191-5.
94. Riebe D, Franklin BA, Thompson PD, Garber CE, Whitfield GP, Magal M, et al. Updating ACSM's Recommendations for Exercise Preparticipation Health Screening. Medicine and science in sports and exercise. 2015;47(11):2473-9.
95. Thompson PD, Arena R, Riebe D, Pescatello LS, American College of Sports M. ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription, ninth edition. Current sports medicine reports. 2013;12(4):215-7.
96. Westcott WL, Winett RA, Annesi JJ, Wojcik JR, Anderson ES, Madden PJ. Prescribing physical activity: applying the ACSM protocols for exercise type, intensity, and duration across 3 training frequencies. The Physician and sportsmedicine. 2009;37(2):51-8.
97. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C, White RD. Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. Diabetes care. 2006;29(6):1433-8.