

Changes in fibrinogen levels, plasma viscosity and insulin resistance after 4 weeks of combined sit-up and walking training

Abbas Ghanbari-Niaki¹ Farhad Ahmadi-Kani Golzar² Ebad Roohbakhsh³ Hossein Ramezani⁴

Professor Department of Exercise Physiology¹, Mazandaran University, Babolsar, Iran. PhD Student of Exercise Physiology², Mazandaran University, Babolsar, Iran. MSc of Exercise Physiology³, Islamic Azad University, Amol Branch, Mazandaran, Iran. MSc of Exercise Physiology⁴, Babol University of Medical Sciences, Mazandaran, Iran.

(Received 27 Dec, 2014

Accepted 20 May, 2015)

Original Article

Abstract

Introduction: Reports concerning the association of physical activity with markers of inflammation, coagulation, and fibrinolysis are ambiguous. The aim of this study was to assess the effect of 4 weeks of combined decomposed sit-up and walking training with two different volumes on fibrinogen, plasma viscosity and insulin resistance index (HOMA-IR) in college, young men.

Methods: In this semi-experimental study, 18 subjects with age range 19 to 25 years selected as research subjects and were randomly divided into two groups including; group 1 (15 min sit-up -30 min run) and group 2 (30 min sit-up -15 min run). The study sit-up training included 25 types of training for abdominal muscles and the walking intensity was 130-140 steps per minute. Blood samples were collected before and after 4 weeks (16 sessions) and the levels of fibrinogen, plasma viscosity and HOMA-IR were measured. Data analyzed by two ways ANOVA (Between-group changes) and paired T-test.

Results: Compared with the pre-test, both groups demonstrated a significant reduction in body weight over the course of the study ($P < 0.05$). BMI for the group 2 (30 minute sit-up +15 minute walking) in the post-test decreased significantly compared with the pre-test ($P = 0.037$). In the post-test fibrinogen levels ($P = 0.008$) and plasma viscosity ($P = 0.008$) decreased significantly only in the group 2. The two-way ANOVA showed a significant difference between the two groups only in the levels of fibrinogen ($P = 0.024$).

Conclusion: The current research findings indicate that fibrinogen and plasma viscosity levels in group 2 (30 minute sit-up +15 minute walking) decreased compared with the pre-test after 4 week of training; but fibrinogen and plasma viscosity levels in the group 1 (15 minute sit-up +30 minute walking) did not change significant.

Correspondence:
Abbas Ghanbari-Niaki, PhD.
Faculty of Physical Education
and Sport Sciences, Mazandaran
University.
Babolsar, Iran
Tel: +98 9111256292
Email:
ghanbara@umz.ac.ir

Key words: Fibrinogen, Plasma, Insulin Resistance

Citation: Ghanbari-Niaki A, Ahmadi-Kani Golzar F, Roohbakhsh E, Ramezani H. Changes in fibrinogen levels, plasma viscosity and insulin resistance after 4 weeks of combined sit-up and walking training. Hormozgan Medical Journal 2016;20(2):104-111.

Introduction:

Sedentary lifestyle is one of the major risk factors for the development of obesity, the metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) (1). Moreover the prevalence of coronary artery diseases is increasing in the young population. Lack of classical risk factors (hyperlipidemia, hypertension, and diabetes mellitus) in some young people affected by myocardial infarction supports the theory that imbalance in the homeostasis system may be a possible etiology for thrombus formation and myocardial infarction (2).

Regular physical activity, on the other hand, has been associated with lower metabolic syndrome and T2DM prevalence even among individuals genetically predisposed to these diseases and with decreased CVD morbidity and mortality (3).

Hemorheology investigates the flow properties of the blood and deformation characteristics of the cellular elements in the blood (4,5). It is argued that the alterations in the hemorheological system play a role in the pathogenesis of many diseases including chronic complications of DM. It has been proven in studies that out of the hemorheological parameters, plasma viscosity is an independent risk factor in many pathologies, such as atherosclerosis, coronary artery disease and peripheral artery disease, in addition to inflammatory diseases (6). Plasma viscosity, fibrinogen concentration and hematocrit are important determinants of blood rheology. The viscosity of plasma increases with increasing protein concentration, but different proteins have different effects on plasma viscosity depending on the shape and size of the protein (7).

Fibrinogen, an acute-phase reactant, is synthesized in the liver. It is an important component of the coagulation pathway and a major determinant of plasma viscosity (8). The Framingham study and other epidemiological studies have shown that fibrinogen is a powerful and independent risk factor for CVD (9). The precise role of fibrinogen in the atherosclerotic process is not yet completely clear; possible explanations include regulation of cell adhesion and proliferation, vasoconstriction at the site of vessel wall injury, stimulation of platelet aggregation and determination of blood viscosity (10).

Insulin resistance (IR) characterized by a decreased capacity of insulin to stimulate glucose uptake in muscles and adipose tissue and in suppression of hepatic glucose production. IR is found to play an important role in the development of MetS. The IR syndrome represents a widely accepted explanation of the classical association of lipid disorders, obesity, impaired glucose tolerance, hypertension and increased cardiovascular risk (11).

There are reports of correlations between insulin resistance and abnormalities of blood rheology and high fibrinogen. An alternative hypothesis assuming that endothelial dysfunction may be in fact the underlying mechanism explaining both insulin resistance and CVD (12,13). Also Perez-Martin et al. showed that insulin sensitivity is statistically associated with two hemorheological parameter: plasma viscosity and red cell aggregability (12).

Sola and colleagues (2007) showed that the rheological disturbances (fibrinogen and plasma viscosity) seem to be associated with insulin resistance and the MetSin obese patients (13).

Physical activity has been suggested to decrease metabolic and CVD risk through its effect on insulin resistance, inflammation, and coagulation (14,15). Although the inverse relationship between physical activity and insulin resistance has been demonstrated in numerous studies, the optimal weekly volume of exercise that may yield beneficial changes on insulin sensitivity is still questionable (3). In a study of Furukawa and colleagues (2008) was shown that 12-week off-site walking program on fibrinogen levels was inconclusive (16).

In another study it was shown that at rest plasma viscosity is lower in physically fit runners than in sedentary normal subjects. They found that plasma viscosity, in the resting state, depended largely on fibrinogen, total globulin, and, hence, total protein concentrations. Fibrinogen and total globulin concentrations at rest were lower in runners than in sedentary subjects (17). This is generally considered to be a rheological advantage, as a less viscous blood and plasma facilitate oxygen delivery across the capillary membrane during exercise (7). Also Ghanbari - Niaki et al., found that 4 weeks of growing pyramidal practice made no significant changes in fibrinogen levels; however, they led to a significant reduction in blood viscosity levels (18).

Against Kilic-Toprak et al. (2012) demonstrated that 3 weeks of progressive resistance exercise training causes decrease in plasma fibrinogen concentrations (19). Dehghan and Faramarzi (2013) showed that 8 weeks low impact aerobic exercise has significant effect on reduction of old women plasma fibrinogen level (20). In another study, Brun et al. (2014) showed a continuum for plasma viscosity which seems to be lower in athletes than low intensity-trained and even more sedentaries.

Therefore, the more an individual perform regular exercise, the lower is his plasma viscosity (21). Furthermore, results of those limited studies are also contradictory or inconclusive. Some studies reported positive effects of exercise training, while others do not report any effects.

A large body of evidence indicates that physical activity is associated with reduced CVD and all-cause mortality in the general population and in subjects with type 2 diabetes. In fact, meta analyses of small-sized studies showed that supervised exercise is effective in improving cardio-respiratory fitness as well as glycemic control and other CVD risk factors (22). Further evidence supports the importance of aerobic exercise for the treatment of patients with type 2 diabetes, including improvements in glycemic control, body composition, coronary heart disease risk factors, and vascular as well as ventricular function (23).

But Poehlman et al. suggest that both endurance and resistance training improve glucose disposal, although by different mechanisms, in young women (24). Patients with type 2 diabetes may also incur additional benefits to glycemic control, body composition, and CVD risk factors by combining aerobic training and resistance training. As such, many organizations recommend the combination of aerobic training and resistance training in all adults, including those with type 2 diabetes (25).

It has been reported that combined aerobic and resistance exercise was reported to be more effective than either one alone on glycemic control (10). Combined strength and aerobic exercise training has been established as the most effective mode in terms of glucose control, insulin action and the modification of cardiovascular risk factors (26). Regarding intensity, one study has shown that low-to moderate-intensity exercise training is as effective as moderate- to high-intensity exercise training (27),

whereas another study reported that high-intensity training was more effective in improving glycemic control (28).

Reports concerning the association of physical activity with markers of inflammation, coagulation, and fibrinolysis are ambiguous (3). In addition, relatively little is known about the influence of low intensity endurance training on insulin resistance and hemorheological parameter, also the results of these studies are equivocal. There is no study that examined the effect of low intensity aerobic training (walking) in combination with various movements of sit-up and activation of the abdominal area on hemorheological changes and insulin resistance. The aim of this study was to assess the effect of 4 weeks of combined decomposed sit-up and walking training with two different volumes on fibrinogen, plasma viscosity and insulin resistance index (HOMA-IR) in college, young men.

Methods:

In a semi experimental protocol, 18 young male students (age: 19-25 years) were randomly selected. A simple random sampling method was used for this purpose. Based on a medical information questionnaire, all subjects were healthy and without any particular problems. In addition, the subjects did not consume any kinds of supplements 6 months prior to the study. Following the ethical committee's approval and with a full description of all risks, each subject gave his informed consent before participation in this study. Then the subjects were randomized into three equal groups of 9 people: experimental group 1 and experimental group 2. The study lasted for a period was 4 week. The desired variables were evaluated twice, once at the beginning and once at the end of the 4 week period. In the first session the subjects got familiar with the working protocol and were asked to perform the movements correctly.

Training was performed for 16 sessions in 4 weeks (4 sessions per week). Every session included a warm-up period (5 minutes), the main program (45 minutes) and a cool-down period (5 minutes). In group 1 the main program included 15 minutes of sit-up exercise, followed by the 30 minutes walking training (15 minute sit-up +30 minute walking). The main program in Group 2 included 30 minutes

of sit-up exercise, followed by the 15 minutes walking training (30 minute sit-up +15 minute walking). Sit-up training in this study consisted of 25 different exercises for the abdominal muscles (29). Walking intensity performed 130 to 140 steps per minute. The number of steps was determined with using a pedometer. Also, subjects were asked to maintain their habitual physical activity throughout the study period (16).

BMI was evaluated by weight (kg) / height (m²) formula. Blood samples were collected to determine resting levels of biochemical variables in the two stages of pre-test (a day before starting the 4 week training course) and post-test (a day after the last training session after the fourth week) under normal room temperature conditions. In order to control the effects of circadian rhythm, blood was taken between 8 and 9 am when the subjects had been fasting for 12 h. 10 cm³ blood samples were taken from the antecubital vein. Plasma was separated 30 minutes after centrifugation at 3000 g at 4°C and stored at -80°C until further analysis. Plasma fibrinogen was evaluated based on Clauss method. Insulin resistance was calculated with the homeostasis model assessment (HOMA-IR) by the following formula: fasting plasma glucose (mmol/L) x fasting serum insulin (μU/mL)/22.5. Plasma viscosity was calculated by the following formula: $1.352 + 0.0167 \times \text{total cholesterol (Mmol/L)} + 0.0285 \times \text{fibrinogen (g/L)} + 0.0045 \times \text{triglyceride (Mmol/L)} + 0.00318 \times \text{hematocrit} - 0.03 \times \text{HDL-C (Mmol/L)}$.

Normality of the data was tested with the Kolmogorov-Smirnov test. Two way ANOVA test with repeated measurements was used to evaluate changes within and between groups (2 groups-2 times). Paired t-test was used to measure within subject significant changes. Statistical significance

level was set at $\alpha \leq 0.05$. SPSS 18 was employed to analyze the data.

Results:

At baseline there were no differences in the age, height, body weight and BMI between the three groups (Table 1).

Table 1. Subject characteristics

	Group 1 (n=9) (15 minute sit-up+30 minute walking)	Group 2 (n=9) (30 minute sit-up+15 minute walking)
Age (y)	21.55 ± 1.81	22.11 ± 1.05
Height (cm)	173.6 ± 5.52	174.3 ± 2.54
Weight (kg)	83.9 ± 12.52	79.34 ± 7.02
BMI (kg/m ²)	27.62 ± 3.42	26.05 ± 2.1

All values are M±SD

Compared with the pre-test, both groups demonstrated a significant reduction in body weight over the course of the study ($P < 0.05$). BMI for the group 2 (30 minute sit-up +15 minute walking) in the post-test decreased significantly compared with the pre-test ($P = 0.037$). But reduction in BMI in group 1 (15 minute sit-up +30 minute walking) was not significant ($P = 0.759$). In the post-test fibrinogen levels ($P = 0.008$) and plasma viscosity ($P = 0.008$) decreased significantly only in the group 2. Fibrinogen and plasma viscosity decreased in the group 1, but these increases were not statistically significant ($P > 0.05$). Finally, in the post-test, no changes were observed in neither groups in comparison with the pre-test ($P > 0.05$) (Table 2).

The two-way ANOVA showed a significant difference between the two groups only in the levels of fibrinogen ($P = 0.024$). However, there was no difference across the groups in other parameters ($P > 0.05$) (Table 2).

Table 2. Changes in body weight, BMI and biochemical parameters before and after the training period

	group (n=9) (15 minute sit-up +30 minute walking)		Group 2 (n=9) (30 minute sit-up +15 minute walking)	
	Pretest	Posttest	Pretest	Posttest
Weight (kg)	83.9±1252	82.1±12.58	79.34±7.02	77.88±7.11
BMI (kg/m ²)	27.62±3.42	27.5±3.82	26.05±2.1	25.56±2.02
Fibrinogen (mg/dl)	244.33±28.12	211.33±31.59	210.11±17.98	175.11±22.05 *, §
Plasma viscosity (mps)	11.25±0.68	10.69±1.37	10.78±0.57	9.83±0.87*
HOMA-IR (molar units)	41.31±11.75	45.85±33.17	41.18±12.19	39.95±13.55

All data are presented as M±SD; * = Significant difference (P<0.05) compare to pretest; § = Significant difference between the groups.

Conclusion:

Epidemiological evidence suggests that abnormalities in the flow properties of the blood, including blood viscosity, hematocrit, plasma viscosity, fibrinogen concentration and red cell aggregation, are associated with cardiovascular complications (7). For example, in a 2- year follow-up study of 600 stroke survivors, blood and plasma viscosity together with fibrinogen concentration were identified as independent risk factors for further major cardiovascular events (30).

The current research findings indicate that fibrinogen and plasma viscosity levels in group 2 (30 minute sit-up +15 minute walking) decreased compared with the pre-test after 4 week of training; but fibrinogen and plasma viscosity levels in the group 1 (15 minute sit-up +30 minute walking) did not change significant. So it seems that more volume of sit-up exercise in group 2 greater influence on the hemorheological parameters.

Decrease in fibrinogen level may cause desirable changes in the blood viscosity, adhesion and platelets aggregation and by reduction of fibrin formation could decrease the risk of arteriosclerosis, thrombosis and CVDs (20).

Current research findings show that body weight amounts in both groups during 4 weeks of combined decomposed sit-up and walking training decreased significantly. Although only in the group 2 BMI decreased significantly.

It seems that Fibrinogen levels affected by weight loss. The findings of studies investigating the effect of weight loss on fibrinogen levels are not conclusive, with a few studies demonstrating a positive effect of weight loss on fibrinogen levels (31,32) and others finding no effect (13). A probable explanation could be that a substantial weight loss, exceeding 10% of initial weight, is needed to produce a significant reduction in

fibrinogen levels (10). Probable mechanisms of reduction in fibrinogen levels, possibly due to increased plasma volume and improve the cardiovascular system (19). Other mechanisms for changes in fibrinogen is increased of the sympathetic nervous system and changes in lipid profiles of subjects (33,34). Some slight decreases fibrinogen can also be attributed to the decrease in lipid profiles. Fibrinogen levels associated with stress, obesity, low density lipoprotein and high-density lipoprotein has an inverse relation. So, high-density lipoprotein and low-density lipoprotein and fat reduction can reduce fibrinogen (18).

Ghanbari -Niaki et al., found that 4 weeks of growing pyramidal practice made no significant changes in fibrinogen levels; however, they led to a significant reduction in blood viscosity levels (18).

Also Kilic-Toprak et al. (2012) demonstrated that 3 weeks of progressive resistance exercise training causes decrease in plasma fibrinogen concentrations; while it was increased on the 4th week (19). Dehghanand Faramarzi (2013) showed that 8 weeks low impact aerobic exercise has significant effect on reduction of old women plasma fibrinogen level (20). However, plasma fibrinogen may be reduced by increasing blood plasma (reduction in viscosity) that helps reduce the risk of atherosclerosis that seems to be the effect of regular exercises (35,36). In another study, Brun et al. (2014) showed a continuum for plasma viscosity which seems to be lower in athletes than low intensity-trained and even more sedentaries. Therefore, the more an individual perform regular exercise, the lower is his plasma viscosity (21).

Differences in exercise protocols, training status of the study subjects and the haemostatic markers used for the assessment of the coagulative and fibrinolytic system may lead to inconsistent results

in studies evaluating the effect of exercise on haemostatic markers (37).

Based on the current research findings, no remarkable changes in insulin resistance index (HOMA-IR) were observed. In similar studies, Jorge et al. (2011) also unable to detect a change in the HOMA index after 12 weeks of combined resistance and aerobic training (38).

The study Stefanov et al. a significant inverse association between physical activity level and HOMA-IR was observed, which is in line with previous reports highlighting the beneficial effect of physical activity on insulin sensitivity in various populations (3). Duncan et al. noted increases in insulin sensitivity of 40% or more in middle-aged, previously sedentary adults after a moderate intensity walking intervention, independent of any changes in BMI or waist circumference (39).

Physical activity has been found to improve insulin sensitivity through changes in body fat mass as well as through fat mass loss-independent mechanisms such as: increased GLUT4 translocation and subsequent glucose utilization in skeletal muscle; improved capacity of skeletal muscle to oxidise fat; increased intramyocellular lipid turnover and decreased quantity of lipid metabolites (3). In another study, Lucotti et al. (2011) reported that compared with aerobic training, combined aerobic and resistance training similarly enhanced body weight loss but exerted less positive effects on insulin sensitivity (40). Recent evidence support a role of resistance exercise in modulating muscle signaling pathways in fasting conditions through an inhibition of Akt/PKB pathway (41). Akt/PKB signaling represents a primary molecular mechanism by which insulin regulates glucose transport in skeletal muscle. Therefore, it is possible that a reduction in Akt/PKB signaling in human skeletal muscle by resistance exercise in the study by Lucotti et al. may explain the only slight improvement in insulin sensitivity observed in combined aerobic and resistance training group while with aerobic training insulin sensitivity was greatly increased (40). These discrepant findings may reflect the different methods used to evaluate insulin sensitivity. For instance, the euglycemic-hyperinsulinemic clamp is more sensitive in estimating insulin action (38).

Some limitations are existed in the present study such as the lack of control group and short duration of the study. Further studies with larger sample sizes and longer period of time are necessary to examine the effect of this type of exercise on hemorheological parameter. It seems that longer durations of training may have more profound effects on hemorheological factors.

In conclusion, 4 weeks of combined sit-up and walking training lead to a reduction in fibrinogen and plasma viscosity, but has no remarkable effect on insulin resistance index. Given that hemorheological disorders involved in several different diseases such as cardiovascular disease have a role, performing this type of training may be beneficial in preventing these diseases. As regards, the prevalence of coronary artery diseases is increasing in the young population; these adaptations were achieved despite a low volume of total exercise suggesting that combined sit-up and walking training is an effective and time efficient exercise strategy to improve health and body weight in young men. Walking and sit-up exercise are eminently suited to physical activity prescription as it requires no special skills or facilities and is achievable by virtually all age groups with little risk of injury.

References:

1. Grøntved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *Jama*. 2011;305(23):2448-2455.
2. Robinson SD, Ludlam CA, Boon NA, Newby DE. Endothelial fibrinolytic capacity predicts future adverse cardiovascular events in patients with coronary heart disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2007;27(7):1651-1656.
3. Stefanov T, Temelkova-Kurktschiev T, Koehler C, Henkel E, Schaper F, Hanefeld M. Association of physical activity with insulin resistance, subclinical inflammation, coagulation, and fibrinolytic biomarkers among population at high risk for type 2 diabetes. *Folia Medica*. 2012;54(2):32-39.

4. Koenig W, Ernst E. The possible role of hemorheology in atherothrombogenesis. *Atherosclerosis*. 1992;94(2):93-107.
5. Isogai Y, Ikemoto S, Kuchiba K, Ogawa J, Yokose T. Abnormal-Blood viscoel. Asticty in diabetic microangiopathy. *Clinical Hemorheology*. 1991;11(3-4):175-182.
6. Aras S, Varli M, Tek I, Cengiz O, Yalcin A, Atli T. The relationship of plasma viscosity with microvascular complications in the diabetic elderly and its predictive value. *European Geriatric Medicine*. 2012;3(5):271-276.
7. Ahmadizad S, El-Sayed MS. The acute effects of resistance exercise on the main determinants of blood rheology. *J Sports Sci*. 2005;23(3):243-249.
8. Kullo IJ, Ballantyne CM, editors. Conditional risk factors for atherosclerosis. *Mayo Clinic Proceedings*. 2005;80(2):219-230.
9. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *Jama*. 1998;279(18):1477-1482.
10. Tzotzas T, Evangelou P, Kiortsis D. Obesity, weight loss and conditional cardiovascular risk factors. *Obes Rev*. 2011;12(5):e282-e289.
11. Chandrasekhar T, Suchitra M, Sachan A, Bitla AR, Rao PS. Indices of insulin resistance in paediatric obesity. *J Clin Sci Res*. 2014;3:7-13.
12. Perez-Martin A, Dumortier M, Pierrisnard E, Raynaud E, Mercier J, Brun J. Multivariate analysis of relationships between insulin sensitivity and blood rheology: Is plasma viscosity a marker of insulin resistance? *Clin Hemorheol Microcirc*. 2001;25(3):91-103.
13. Sola E, Vaya A, Simo M, Hernandez-Mijares A, Morillas C, Espana F, et al. Fibrinogen, plasma viscosity and blood viscosity in obesity. Relationship with insulin resistance. *Clin Hemorheol Microcirc*. 2007;37(4):309-318.
14. Mora S, Cook N, Buring JE, Ridker PM, Lee I-M. Physical activity and reduced risk of cardiovascular events potential mediating mechanisms. *Circulation*. 2007;116(19):2110-2118.
15. Jeon CY, Lokken RP, Hu FB, Van Dam RM. Physical Activity of Moderate Intensity and Risk of Type 2 Diabetes A systematic review. *Diabetes Care*. 2007;30(3):744-752.
16. Furukawa F, Kazuma K, Kojima M, Kusukawa R. Effects of an off-Site walking program on fibrinogen and exercise energy expenditure in women. *Asian Nursing Research*. 2008;2(1):35-45.
17. Letcher R, Pickering T, Chien S, Laragh J. Effects of exercise on plasma viscosity in athletes and sedentary normal subjects. *Clin Cardiol*. 1981;4(4):172-179.
18. Ghanbari-Niaki A, Behzad Khameslo M, Tayebi SM. Effect of Pyramidal Training on Plasma Lipid Profile and Fibrinogen, and Blood Viscosity of Untrained Young Men. *Annals of Applied Sport Science*. 2013;1(3):47-56.
19. Kilic-Toprak E, Ardic F, Erken G, Unver-Kocak F, Kucukatay V, Bor-Kucukatay M. Hemorheological responses to progressive resistance exercise training in healthy young males. *Med Sci Monit*. 2012;18(6):CR351-CR360.
20. Dehghan S, Faramarzi M. The effect of 8-week low impact aerobic exercise on plasma fibrinogen concentration in old women. *International Journal of Applied Exercise Physiology*. 2013;2(1):40-45.
21. Brun J-F, Varlet-Marie E, Chevance G, Pollatz M, Fedou C, de Mauverger ER. Versatility of 'hemorheologic fitness' according to exercise intensity: emphasis on the "healthy primitive lifestyle". *Korea-Australia Rheology Journal*. 2014;26(2):249-253.
22. Balducci S, Zanuso S, Cardelli P, Salvi L, Bazuro A, Pugliese L, et al. Effect of high-versus low-intensity supervised aerobic and resistance training on modifiable cardiovascular risk factors in type 2 diabetes; the Italian Diabetes and Exercise Study (IDES). *PloS one*. 2012;7(11):e49297.
23. Pate RR, Davis MG, Robinson TN, Stone EJ, McKenzie TL, Young JC. Promoting physical activity in children and youth a leadership role for schools: A scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism (Physical Activity Committee) in collaboration with the councils on Cardiovascular Disease in the Young and Cardiovascular Nursing. *Circulation*. 2006;114(11):1214-1224.
24. Poehlman ET, Dvorak RV, DeNino WF, Brochu M, Ades PA. Effects of Resistance Training and Endurance Training on Insulin Sensitivity in Nonobese, Young Women: A Controlled

- Randomized Trial 1. *Clin Endocrinol Metab.* 2000;85(7):2463-2468.
25. Johannsen NM, Swift DL, Lavie CJ, Earnest CP, Blair SN, Church TS. Categorical Analysis of the Impact of Aerobic and Resistance Exercise Training, Alone and in Combination, on cardiorespiratory fitness levels in patients with type 2 diabetes results from the HART-D study. *Diabetes Care.* 2013;36(10):3305-3312.
26. Touvra AM, Volaklis KA, Spassis AT, Zois CE, Douda H, Kotsa K, et al. Combined strength and aerobic training increases transforming growth factor-beta1 in patients with type 2 diabetes. *Hormones (Athens).* 2011;10(2):125-130.
27. Hansen D, Dendale P, Jonkers R, Beelen M, Manders R, Corluy L, et al. Continuous low-to moderate-intensity exercise training is as effective as moderate-to high-intensity exercise training at lowering blood HbA1c in obese type 2 diabetes patients. *Diabetologia.* 2009;52(9):1789-1797.
28. Dunstan DW, Daly RM, Owen N, Jolley D, De Courten M, Shaw J, et al. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care.* 2002;25(10):1729-1736.
29. Schilling JF, Murphy JC, Bonney JR, Thich JL. Effect of core strength and endurance training on performance in college students: Randomized pilot study. *J Body Mov Ther.* 2013;17(3):278-290.
30. Ernst E, Dabur L, Saradeth T. The kinetics of blood rheology during and after prolonged standardized exercise. *Clinical Hemorheology and Microcirculation.* 1991;11(5):429-439.
31. Ditschuneit HH, Flechtner-Mors M, Adler G. Fibrinogen in obesity before and after weight reduction. *Obes Res.* 1995;3(1):43-48.
32. Marckmann P, Toubro S, Astrup A. Sustained improvement in blood lipids, coagulation, and fibrinolysis after major weight loss in obese subjects. *Eur J Clin Nutr.* 1998;52(5):329-333.
33. Smith J. Effects of strenuous exercise on haemostasis. *Br J Sports Med.* 2003;37(5):433-435.
34. Smith J, Garbutt G, Lopes P, Pedoe DT. Effects of prolonged strenuous exercise (marathon running) on biochemical and haematological markers used in the investigation of patients in the emergency department. *Br J Sports Med.* 2004;38(3):292-294.
35. Lambert CP, Evans WJ. Adaptations to aerobic and resistance exercise in the elderly. *Rev Endocr Metab Disord.* 2005;6(2):137-143.
36. Desouza CA, Dengel DR, Rogers MA, Cox K, Macko RF. Fibrinolytic responses to acute physical activity in older hypertensive men. *Journal of Applied Physiology.* 1997;82(6):1765-1770.
37. Ali PN, Hanachi P. To investigate the fibrinogen and some of coagulation factors in anaerobic exercise training women. *World Applied Sciences Journal.* 2011;12(1):72-75.
38. Jorge MLMP, de Oliveira VN, Resende NM, Paraiso LF, Calixto A, Diniz ALD, et al. The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus. *Metabolism.* 2011;60(9):1244-1252.
39. Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care.* 2003;26(3):557-562.
40. Lucotti P, Monti LD, Setola E, Galluccio E, Gatti R, Bosi E, et al. Aerobic and resistance training effects compared to aerobic training alone in obese type 2 diabetic patients on diet treatment. *Diabetes Res Clin Pract.* 2011;94(3):395-403.
41. Deldicque L, Atherton P, Patel R, Theisen D, Nielens H, Rennie MJ, et al. Decrease in Akt/PKB signalling in human skeletal muscle by resistance exercise. *Eur J Appl Physiol.* 2008;104(1):57-65.