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RESEARCH ARTICLE

Effect of aerobic exercises on blood coagulation and fibrinolytic system in type 2 diabetic patients

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Abstract

Background: Diabetes is a major worldwide health problem. It is associated with the long-term vascular complications particularly cardiovascular disease which is the commonest cause of death in diabetic patients. Abnormalities in endogenous coagulation and fibrinolysis may play an important role in the risk of acute cardiovascular event. Regular physical activity is associated with decrease in all causes of mortality especially cardiovascular disease. So, the current study was carried out to investigate the effect of aerobic exercises on blood coagulation and fibrinolysis in type 2 diabetic patients. **Subjects and Methods:** This study was conducted on fifty type 2 diabetic male patients. All were randomly selected from outpatients' clinic of Zagazig University hospitals. The included subjects were subdivided into two equal groups (25 patients for each). The first group (group A) received a low calorie diet without aerobic exercise and the second group (group B) received a low calorie diet with a program of aerobic exercise in addition to the standard treatment of the diabetic state. All patients subjected to full history and clinical examination and routine laboratory investigations including random blood glucose و glycosylated haemoglobin (HbA1c), liver and kidney function tests. In addition to measurement of prothrombin time, fibrinogen, tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1(PAI-1) before starting program and after the end of program (12 weeks). **Results:** The present study showed that both groups were matched with each other as regard to age, HA1c ,and coagulation profiles before the start of the study ,and An aerobic exercises with low calorie diet significantly increase each of prothrombin time, and tissue plasminogen activator and significantly decrease each of fibrinogen and plasminogen activator inhibitor-1 levels in group B .while there was no significantly difference in the previous parameters in group A without aerobic exercise. In pretreatment status there was no significant difference in the previous parameters between groups A and B .while in posttreatment status there was significant increase each of prothrombin time and tissue plasminogen activator and significantly decrease each of fibrinogen and plasminogen activator inhibitor-1 levels in group B as compared to group A. **Conclusion:** We conclude that low-calorie diet with aerobic exercise is more effective than the low-calorie diet only for reducing blood coagulation and increasing fibrinolysis in type 2 diabetes on a short term program (up to twelve weeks), and this may lead to protection against cardio vascular events on along term and further studies can be performed to show the efficacy of anaerobic versus aerobic exercise on blood coagulation in diabetic patients.

INTRODUCTION

Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs especially heart, kidney and blood vessels [(1)]. Insulin resistance is directly involved in pathogenesis of type 2 diabetes and hypertension [(2)] . Diabetes has an increased incidence of atherosclerotic, cardiovascular, peripheral vascular, cerebrovascular disease and hypertension complications [(3)] . Exercise is an insulin-independent stimulus for increased glucose uptake by the working muscle cells via the GLUT-4 transporter. Findings from exercise training studies support the concept that aerobic and anaerobic exercise training regimens improve glucose uptake and insulin sensitivity [(4)] . Exercise promotes a healthy cardiovascular system and improves endothelial functions by reducing adiposity, blood pressure, diabetes incidence, dyslipidemia, and inflammation enhancing insulin sensitivity, glycemic control and fibrinolysis [(5)] . Shear-induced platelet aggregation (SIPA) is important in arterial thrombosis which is a major contributing factor for atherothrombotic occlusion of blood vessels which can be inhibited by exercise training [(6)].An effective aerobic exercise include any repetitive, rhythmical, relatively low intensity exercise involving large muscle groups with frequency of 3-6 days per week, duration 20-60 min and should involve 5-10 minutes of warming up, followed by at least 20 minutes of exercise at an intensity of 70-80% of maximum heart rate, ending with 5-10 minutes of cooling down at an intensity of 50-60% of maximum heart rate and should begin slowly and gently increase the amount gradually as jogging, brisk walking, cross-country skiing, swimming, cycling [(7)]. Regular physical activity has a mild or moderate effect on numerous metabolic and cardiovascular risk factors that constitute or related to the metabolic syndrome [(8)], including regulation of body weight, reduction of (insulin resistance, hypertension and dyslipidemia) and enhancement of (insulin sensitivity, glycemic control, fibrinolytic and endothelial function) [(9)] . Increased physical activity is the first line intervention for preventing and treating patients with prehypertension. Two types of exercise effects are significant – acute effects and chronic effects. Acute effects: there is an average reduction in BP of 5–7 mmHg immediately after an exercise session. This is referred to as post exercise hypotension (PEH). While PEH occurs in both normotensive and hypertensive patients, a greater PEH is seen in hypertensive. The PEH effects can occur for up to 22 hours regardless of the exercise intensity. Chronic effects: the average BP reduction with regular exercise for hypertensives not normalized by drug is 7.4/5.8 mmHg. If baseline BP is normal because of drug therapy, the average decrease was an additional 2.6/1.8 mmHg irrespective of drug therapy type [(10)]. The preventive effect of physical activity is greatest in subjects with a high risk of diabetes. Physical activity is beneficial also in subjects who already have diabetes by favorably influencing the risk factors of other chronic diseases, by decreasing the need of drug treatment, by improving fitness and mood and by decreasing morbidity and mortality [(11)]. Both moderate to vigorous aerobic activities as well as resistance training are effective and it is recommendable to practice them in combination. Exercise training also shows beneficial effects on insulin resistance syndrome found in children [(12).] Exercise increases insulin sensitivity of muscle glucose transport and also enhances insulin action in extra muscular tissues. The most important endocrine responses to exercise include an increase in sympathetic nervous activity causing changes in insulin counter-regulatory hormones [(13)] .The protective effects of exercise result from both short term and long term effects of contractile activity on the regulation of glucose metabolism by skeletal muscle. These effects range from the insulin independent stimulation of glucose transport induced by exercise, to acute and chronic alterations in the biological effectiveness of insulin in muscle [(14)].Exercise can regulate blood glucose levels through three distinct mechanisms: acute stimulation of muscle glucose transport; acute enhancement of insulin action, and long term up regulation of the insulin signaling pathway resulting from regular exercise training [(7)] hypercoagulation and endothelial dysfunction. Platelet dysfunction has attired attention as a potential cause of increased cardiovascular morbidity and mortality in essential hypertension. All the above suggest the importance of platelet function in coronary artery disease and hypertension [(15).] Short term exercise is usually associated with a significant shortening of activated partial thromboplasmin time (APTT) and a marked increase in factor VIII (FVIII). The rise in FVIII is directly related to exercise intensity and the individuals' training status [(16).] Exercise also induces a significant increase in blood fibrinolysis which is dependent on exercise intensity, duration and training condition. The rise in blood fibrinolysis is mainly due to an increase in tissue-type plasminogen activator (t-PA) and a decrease in its main inhibitor plasminogen activator inhibitor-1 (PAI-1) which is released from the endothelial cells of the vessel wall [(17).] Therefore, acute responses to exercise may increase the risk of ischaemic event. However, chronic aerobic exercise training may decrease coagulation potential and increase fibrinolytic potential in both healthy individuals and CVD patients. Due to the aforementioned importance of resting

fibrinolysis on the fibrinolytic response to exercise, chronic aerobic exercise training may cause favorable adaptations that could contribute to decreased risk for ischaemic event, both at rest and during physical exertion [18]. Therefore The present study was designed to study the effect of aerobic exercises (40-50 minutes walking exercise 3 times/week) with low calorie diet versus low calorie diet without exercise training on prothrombin time, fibrinogen plasminogen activator inhibitor-1(PAI-1) and tissue plasminogen activator (tpA) on fifty diabetic patients. **Subjects:** Fifty type 2 diabetic male patients with age ranged from 40 to 50 years were randomly selected from outpatients' clinic of Zagazig University hospitals; in the period from 1st January to march 31, 2014. Our study is interventional randomized study included fifty subjects were subdivided into two equal groups. Each group consisted of twenty five patients. The first group (group A) received a low calorie diet without aerobic exercise and the second group (group B) received a low calorie diet with a program of aerobic exercise. The duration of diabetes was ranged from 5 to 7 years. And a written informed consent form was signed by the patients to participate in our study.

Exclusion Criteria: Subjects with hepatic, renal, Cardiac, Chest diseases, and endocrinal disorder as well as musculoskeletal disease and other disorder that may affect the result of the study were excluded. They were non smokers and non obese (BMI is less than 30). All patients subjected to full clinical history and full clinical examination, routine laboratory investigations including random blood sugar, HBA1c, liver and kidney function tests. In addition to Blood coagulation that included (prothrombin time fibrinogen, tissue plasminogen activator, and plasminogen activator inhibitor-1 (PAI-1)) were recorded in the two groups at two intervals; the starting of the experiment (pre) and the end of 12 weeks (post-program). **Methodology of exercises program:**

1. The steps of training are explained for each patient.
2. Designing nutrition plan for each subject in both groups (Low calorie diet model). All subjects in the study (group B) attended the program of walking for twelve weeks according to the following parameters:-

***Mode of exercise:** aerobic exercise.
***Intensity** according to heart rate (60-75% of maximum heart rate) MHR=220-age.
***Heart rate:** determined by sensor of treadmill.
***Duration:** 40-50 min per session. Each session consisted of 5-10 minutes warming up exercise on treadmill without increasing speed or intensity and the same for cooling down phase. There were 30 minutes conditioning exercise including increasing the speed of treadmill till reaching (60-75%) of maximum heart rate.
***Frequency:** 3 times/week for 12 weeks.
After 12 weeks program, another blood samples were taken. Prothrombin time, fibrinogen and plasminogen activator inhibitor-1 were measured and then pre and post samples were compared. **Statistical Analysis**: Data was collected and changes in prothrombin time fibrinogen and plasminogen activator inhibitor-1 were assessed using independent t-test to compare between the two groups and dependent t-test was used to assess changes within group using statistical package of social sciences (SPSS) for windows version 17**.** A P-value ≤ 0.05 was considered statistically significant [19].

Results:

Table (1): General Demographic and laboratory data of patients in both groups (A&B):

General characteristics	Group A (Mean ±SD)	Group B (Mean ±SD)	t	P
Age (yrs)	44.86±2.92	44.2±3.1	0.59	0.55
Random blood glucose level (mg/dl)	204.13±16.91	208.53 ±13.14	0.79	0.43
HbA1c (%)	7.88±1.2	8.1±1.15	0.38	0.68
Prothrombin Time (sec)	13.09 ±0.63	13.05±0.73	0.16	0.86
Fibrinogen level (mg/dl)	242.53±33.58	242.8 ±40.15	0.02	0.98
Tissue plasminogen activator (IU/ml)	0.66±0.23	0.66±0.35	0.45	0.67
Plasminogen activator inhibitor-1 (mg/dl)	110.13 ±15.55	110.67 ±13.36	0.1	0.92

Table (2): Comparison of Mean value and ±SD of Prothrombin time, Fibrinogen level, tissue plasminogen activator and plasminogen activator inhibitor-1 level in pre and post treatment between group A and group B:

	Group A (Mean ±SD)				**Group B** (Mean ±SD)			
	Pretreatment	Posttreatment	**t**	**P**	Pretreatment	Posttreatment	**t**	**P**
Prothrombin Time (sec)	13.09±0.63	13.11±0.65	0.71	0.48 **NS**	13.05±0.73	13.61±0.631	5.25	0.0001

Fibrinogen Level (mg/dl)	242.03±33.58	242.33±33.08	0.36	0.71 **NS**	242.8±40.15	214.6±34.51	10.1	0.0001
Tissue plasminogen Activator (IU/ml)	0.66±0.23	0.67±0.29	1.13	0.58 **NS**	0.66±0.35	0.79±0.16	6.34	0.0001
Plasminogen activator inhibitor-1 (mg/dl)	110.13±15.13	109.8±15.58	1.16	0.26 **NS**	110.67±13.06	99.63±11.4	7.43	0.0001

Discussion:

Metabolic syndrome is defined by clustering of several cardiovascular risk factors, including impaired glucose tolerance, diabetes, hypertension, dyslipidemia, and visceral obesity [(20)]. The insulin resistance syndrome that precedes the onset of overt diabetes is associated with metabolic alterations and abnormalities in hemostasis. Impaired fibrinolysis is found in impaired glucose tolerance and type 2 diabetes, associated with components of metabolic syndrome [(21)]. A number of hemostatic changes occur with exercise that involves blood platelets, coagulation factors, and fibrinolysis. Both acute and chronic exercise regimens influence these markers of blood homeostasis. Because acute exercise is thought to increase platelet aggregation, concerns have been raised regarding exercise as a potential trigger for thrombosis-related cardiac events [(22).] However, such events are rare during exercise, there is considerable individual variability in the response to acute exercise, and these responses are dependent on exercise intensity, suppressed by β-blockade, enhanced by catecholamine responses, and more pronounced among patients with coronary artery disease [(4)]. In contrast to acute exercise, both higher physical activity patterns and structured exercise programs have an inhibitory effect on thrombogenic factors and enhance blood fibrinolytic potential [(23)]. These changes have been demonstrated in both healthy subjects and patients with diabetes. Therefore, the present study was designed to study the effect of aerobic exercises (40-50 minutes walking exercise 3 times/week) with low calorie diet versus low calorie diet without exercise training on prothrombin time, fibrinogen, tissue plasminogen activator and plasminogen activator inhibitor-1 on Fifty diabetic male subjects (type 2). Our results showed that aerobic exercises with low calorie diet had greater effect to increase prothrombin and tissue plasminogen activator when compared with low calorie diet without exercise. And while aerobic exercises with low calorie die had greater effect to decrease both fibrinogen and plasminogen activator inhibitor-1 levels when compared with low calorie diet without exercise. The present study examined the hypothesis that combining a regime of moderate aerobic exercise with one daily fish meal as part of low fat diet, would improve coagulation and fibrinolytic factors in dyslipidaemic type 2 diabetic patients. In randomized controlled 8-weks trial, sedentary type 2 diabetic subjects were assigned to a low fat diet (30% daily energy intake and further randomized to moderate exercise program. Plasma levels of fibrinogen, plasminogen activator inhibitor-1. Antigen was measured before and after intervention by enzyme immunoassays (ELISA) [(24)] there is decrease in plasminogen activator inhibitor-1 and fibrinogen; this may reduce thrombotic potential and decrease cardiovascular risk. In agreement with present study a study performed by National Institute of Health [(25)] approved that regular moderate intensity physical exercise decreases platelet aggregability as a consequence of increasing levels of plasminogen activator inhibitor-1. In addition, the exercise-associated improvement in the lipid profile and reduction in fat mass may decrease blood coagulation as well as increase fibrinolysis thus it can be hypothesized that physical exercise training has a powerful beneficial impact on blood coagulation and fibrinolysis. Similarly, Juhan et al**.** [(26)] approved that the metabolic syndrome is associated with an increased risk for the development of cardiovascular diseases, a number of haemostatic abnormalities have recently be associated with metabolic syndrome, amongst with elevation of plasminogen activator inhibitor-1 and also with fibrinogen concentration. It's concluded that moderate intensity exercise induces favorable changes in metabolic syndrome in lowering lipid profile and plasminogen activator inhibitor levels and may reduce risk of cardiovascular diseases. Also Hilberg et al. [(27)] approved that a number of hemostatic changes involving platelets, coagulation and fibrinolysis have been reported after acute physical exercise. Results have sometimes been controversial, due to differences in subjects investigated type of exercise and methods used for hemostatic evaluation, on the whole, physical exercise has been shown to induce; Inactivation of coagulation leading to slight but significant thrombin generation and activation of fibrinolysis, a few data are available on the effects on platelets whereas studies performed on fibrinolysis shows a decrease in plasminogen activator inhibitor. Another study by Lowe [(28)] stated that strenuous exercise was associated with lower fibrinogen concentrations than mild exercise, implying a difference of about 15% in the risk of ischaemic heart disease. Strenuous exercise was also associated with lower cholesterol concentrations. More frequent strenuous exercise was associated with

lower factor VII activity. With the recognition of plasma fibrinogen as a strong index of ischaemic heart disease risk, the results of this and other studies suggest a pathway through which the protective effect of strenuous exercise may partly be mediated and they provide doctors and patients with a valuable incentive towards prevention, particularly in those whose risk of ischaemic heart disease is substantially due to raised fibrinogen concentrations. On the other hand, Lamprecht et al.[29] aimed to identify the effect of walking exercise on whole blood clotting time was measured before and after four different intensities and duration of exercise using 21 male colleague students and subjects. The exercise consisted of a 15-min. walk on a motor-driven treadmill at 2.5 M.P.H. and a steeping exercise at 12-inch bench, 30 steps per minute for 15 min. No statistically significant variation was found on whole blood clotting time of samples drawn before and after exercise. It was concluded that, in general exercise was not followed by hypercoagulability. However, in some subjects thrombin generation rate was increased due to undetermined factors. Similarly, Ferguson and Guest [30] approved that both the coagulation and fibrinolytic cascades are stimulated by strenuous exercise but the temporal relation between the two and its clinical significance to be clarified. Doctors and athletes should be aware of the haemostatic changes induced by exercise, and further work is needed to classify the possible role of these changes in sudden cardiac death. In contrast to our study Jensen et al. [31] concluded that there were no significant changes in PAI-1 Ag, tPA Ag and PAI-1 activity from baseline to the end of the follow-up period in either the diet-only or diet-plus-exercise group compared with the control group. There was no change in fibrinogen level after the 12 weeks of intervention. However, fibrinogen was significantly decreased from baseline to the end of the follow-up period in the diet-only and diet-plus-exercise groups compared with the control group due to a non-significant increase during the follow-up period in the control group. There was no significant differences between changes in the diet-only and diet-plus-exercise groups in PAI-1 activity or PAI-1 Ag , tPA Ag, or fibrinogen levels after the intervention or at follow-up (P>.05) . A possible mechanism could be a positive effect of the dietary intervention on thrombogenesis through decreased coagulation (lowering of fibrinogen) and increased fibrinolysis (lowering of PAI-1 activity).

Finally we concluded that regular exercise and low calorie diet providing no more than one third of energy from fats have been recommended for the prevention of atherosclerosis diseases. The background for these guidelines is the key role of plasma lipids. However, the importance of thrombogenesis in acute myocardial infarction has become obvious during the last decade. Hyperlipidaemia and excess of adipose tissue increase blood coagulation and decrease fibrinolysis. It can be hypothesized that moderation in physical activity and diet carries a more powerful impact on blood coagulation and fibrinolysis than either lifestyle modification alone. Exercises have an effect on improving coagulation by increasing prothrombin time and decreasing fibrinogen level and also on fibrinolysis by decreasing plasminogen activator inhibitor-1 and increasing tissue plasminogen activator.

Consequently, increased physical activity is now strongly recommended as part of the lifestyle modifications as an adjunct to pharmacological therapy proposed by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and recent European Society of Hypertension/European Society of Cardiology guidelines [32].

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