Effect of Exercise on Plasminogen Activator Inhibitor-1(PAI-1) Level in Patients with Metabolic Syndrome

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Abstract: *Back ground and aim:* Metabolic syndrome is a group of interrelated risk factors, accurate clinical diagnosis and treatment is mandatory for detection of population at risk for coronary heart disease and diabetes. Physical exercise protects against the development of cardiovascular disease, partly by lowering plasmatic total cholesterol, LDL and increased HDL .In addition it is now established that increased C - reactive protein (CRP) and plasminogen activator inhibitor-1(PAI-1) play a role in the maintenance of an inflammatory state and in the development of cardiovascular disease. This study aimed to compare plasma levels of LDL, HDL, CRP, and PAI-1 in patients with metabolic syndrome before and 6 months after moderate intensity exercise. **Methods:** Forty five obese non smoker, males with metabolic syndrome living sedentary life were included in the study .Blood samples were collected at the beginning of the study and 6 months later. However only 42 patients completed in our study The plasma lipid profile (Triglycerides, HDL, LDL, total cholesterol), fasting blood glucose, C - reactive protein and PAI-1 levels were determined. Body weight and BMI were also measured before and after the exercise. **Results:** Total cholesterol ,LDL,HDL,triglycerides,CRP,PAI-1 levels were lower after moderate intensity exercise in relation to levels before moderate intensity exercise($p<0.05$).In addition we observed a positive correlation between PAI-1 and LDL after exercise($r=0.301$,$p=0.053$),PAI and triglycerides after exercise($r=0.286$,$p=0.066$), negative correlation between HDL and PAI-1($r=-0.315$,$p=0.042$). These results indicate that moderate intensity exercise induces favourable changes in metabolic syndrome in lowering lipid profile and PAI-1 levels and may reduce risk of cardiovascular diseases.

[Serag Esmat, Randa F Abd Al Salam, Laila Rashed. **Effect Of Exercise On Plasminogen Activator Inhibitor-1(PAI-1) Level In Patients With Metabolic Syndrome**. Journal of American Science 2010;6(12):1374-1380]. (ISSN: 1545-1003). http://www.americanscience.org.

Keywords: Metabolic syndrome, PAI-1, exercise

1. Introduction

Metabolic syndrome is a cluster of metabolic abnormalities and related clinical syndromes most important of which are coronary artery disease and type 2 diabetes mellitus, insulin resistance, visceral adiposity, dyslipidaemia and chronic subclinical proinflammatory state are the main characteristic features of metabolic syndrome. These inflammatory process include increase in plasma proinflammatory cytokines as tumor necrosis factor alpha (TNF-$\propto$),plasminogen activator inhibitor type-1 (PAI-1), C-reactive protein (CRP) ,Interleukin 6 (IL-6) and reduction of anti-inflammatory cytokines as interleukin 10 (IL-10) and adiponectin [(1, 2)]
Sedentary lifestyle is characterized by alterations in pro-inflammatory markers in the plasma [(3,4)].

The haemostatic abnormality most likely linked to insulin resistance is the elevation of circulating plasminogen activator inhibitor-1(PAI-1).Increased PAI-1 level can be now considered a true component of the syndrome and increases risk of developing cardiovascular disease [(5)].

The aim of this study is to compare plasma levels of LDL, HDL, CRP, and PAI-1 in patients with metabolic syndrome before and 6 months after moderate intensity exercise.

2. Patients and methods:

In a cross sectional study forty five obese, non-smoker men with metabolic syndrome, participated in this study .All subjects were living sedentary life, age (30-49 years),BMI ≥30 ,all patients under went complete history taking, family history of diabetes and personal medical history, history of smoking, physical activity of each subject was defined as either sedentary (<150 min/week) or active (>150min/week) . Patients selection based on International Diabetes Federation(IDF) [(6)] ,metabolic syndrome was defined as central obesity (waist circumference ≥94 cm for men and ≥80cm for women),along with two or more of the following criteria (1) hypertriglyceridemia

(serum triglycerides ≥1.7 mmol/l(150 mg/dl) or current treatment with fibrates (2) an abnormally low HDL cholesterol concentration (<1.03mmol/l for men(<40 mg/dl) and <1.29 mmol/l for women(<50 mg/dl)(3) elevated blood pressure (systolic blood pressure ≥130mmhg and/or diastolic blood pressure≥85mmhg or current use of antihypertensive drugs or (4)elevated fasting glucose ≥5.6 mmol/l (≥100 mg/dl)or previous diagnosis of diabetes. All underwent physical examination including blood pressure recording and anthropometric measurement (BMI, waist circumference). Blood samples of all patients for fasting blood sugar, CRP, total cholesterol, triglycerides, HDL, LDL, PAI-1 were stored at -20^{0}c until analysis. Physical examination and blood samples were collected after 6 months of moderate intensity physical exercise. Only 42 patients completed in the study .The benefits and risks were explained to all patients .They all gave their oral approval to participate in the study.

Blood samples collected after an overnight fast of at least 10 h, stored at -20^{0}c until analysis.
Lipid profiles assay. total cholesterol, triglycerides and HDL were assessed by enzymatic methods using commercially available kits LDL was estimated by Friedewald formula (LDL= total cholesterol-(HDL+triglyceride/5). plasma CRP was measured by kit supplied by (Roche Diagnostics, Indianapolis, IN) and PAI-1was assessed by ELISA kit (Trinity Biotech USA, St. Louis, MO) according to manufacturer instruction .

3. Statistical Methodology:

Data were statistically described in terms of mean ± standard deviation (± SD). Comparison between pre and post data was done using paired *t* test. Correlation between various variables was done using Pearson moment correlation equation for linear relation. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, and USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows

4. Results:

Results were illustrated in the form of 3 tables. Table 1 shows the mean value of patient anthropometric data(WT, BMI and Waist circumference) and the mean value of the laboratory data(PAI-1, FBS, Total cholesterol, HDL, LDL, CRP and Triglycerides), the table also shows the mean values of systolic and diastolic blood pressure of all patients before exercise.

Table 1: patient anthropometric and lab data before exercise

Parameter	Mean value of the parameters of the 42 patients
Wt(kg)	101.45
BMI(kg/m^2)	31.71
Waist(cm)	105.19
PAI-1(ng/ml)	19.279
FBS(mg/dl)	94.21
Chol(mg/dl)	233.00
HDL(mg/dl)	46.10
LDL(mg/dl)	166.40
TGs(mg/dl)	128.90
SBP(mm hg)	140.12
DBP(mm hg)	87.98
CRP(g/l)	4.12

Table 2: showing comparison in anthropometric and lab data before and after exercise (BMI, lipid profile, CRP, PAI-1) in patients before and after 6 month moderate intensity exercise. In comparison between before and after exercise all parameters show significant difference before and after exercise.

Table 2: Comparison between patient's data before and after exercise.

Parameter	Mean value before exercise	Mean value after Exercise	Correlation	p value
Wt(kg)	101.45	90.45	0.341	0.027*
BMI(kg/m^2)	31.71	28.681	0.816	0.000**
Waist(cm)	105.19	98.60	0.850	0.000**
PAI-1(ng/ml)	19.279	10.379	0.414	0.006*
FBS(mg/dl)	94.21	85.69	0.655	0.000**
Chol(mg/dl)	233.00	209.00	0.804	0.000**
HDL(mg/dl)	46.10	54.45	0.421	0.006*
LDL(mg/dl)	166.40	136.10	0.768	0.000**
TGs(mg/dl)	128.90	108.60	0.909	0.000**
SBP(mm hg)	140.12	133.93	0.665	0.000**
DBP(mg/dl)	87.98	83.81	0.434	0.004*
CRP(g/l)	4.12	2.51	0.906	0.000**

*p is significant p<0.05
**p is highly significant p<0.001

Table 3: Showing correlations between PAI-1 and different lab data 6 month after moderate intensity exercise. Positive correlation between PAI-1 and LDL(r=0.301, p=0.053), PAI and triglycerides (r=0.286, p=0.066) PAI-1 and BMI (p<0.001,r=0.589) , negative correlation between HDL and PAI-1(r=-0.315, p=0.042). Negative not statistically significant correlation between CRP and PAI-1(r=-0.016, p=0.921)

Table 3: Correlation of PAI-1 to different data before and after exercise.

		PAI-1-Pre	PAI-1-Post
Wt(kg)	Pearson Correlation	0.116	0.053
	p value	0.464	0.737
BMI(kg/m^2)	Pearson Correlation	0.507	0.589
	p value	0.001*	0.000****
Waist(cm)	Pearson Correlation	0.529	0.370
	p value	0.000**	0.016*
FBS(mg/dl)	Pearson Correlation	0.708	0.367
	p value	0.000**	0.017*
Chol(mg/dl)	Pearson Correlation	0.184	0.173
	p value	0.245	0.274
HDL(mg/dl)	Pearson Correlation	0.029	-0.315
	p value	0.855	0.042
LDL(mg/dl)	Pearson Correlation	0.336	0.301
	p value	0.030*	0.053*
TGs(mg/dl)	Pearson Correlation	0.236	0.286
	p value	0.133	0.066*
SBP(mm hg)	Pearson Correlation	0.375	0.066*
	p value	0.015	0.676
DBP(mm hg)	Pearson Correlation	0.169	0.070*
	p value	0.285	0.660
CRP(g/l)	Pearson Correlation	0.147	-0.016
	p value	0.354	0.921

*p is significant p<0.05
**p is highly significant p<0.001

5. Discussion:

The metabolic syndrome is associated with an increased risk for the development of cardiovascular disease [7,8], A number of haemostatic abnormalities have recently been associated with the metabolic syndrome ,amongst with elevated concentrations of plasminogen activator inhibitor -1(PAI-1) and tissue plasminogen activator antigen(tPA_{ag}) share the strongest associations and have been studied in the most detail [9]. Consistent associations have also been found with fibrinogen concentrations, vitamin K dependant coagulation factors (factors-vii,ix and x) ,C-reactive protein (CRP) and von willebrand factor (vWF syndrome [10, 11], increase in plasma proinflammatory cytokines as tumor necrosis factor alpha (TNF- ∝) ,Interlukin 6 (IL-6) and reduction of anti-inflammatory cytokines as interleukin 10 (IL-10) and adiponectin [1, 2]. It is now well established that impaired fibrinolysis due to elevated PAI-1 activity ($PAI\text{-}1_{act}$) is an important feature of the metabolic syndrome. [19].

PAI-1, produced by vascular endothelium is an important risk factor for CAD .Increased PAI-1levels may predispose patients to the formation of atherosclerotic plaques prone to rupture with a high lipid –to-vascular smooth muscle ratio as a result of decreased cell migration [12] Circulating levels of PAI-1 are increased in obese subjects with metabolic syndrome, as well as in patients with type2diabetes.The plasma levels of PAI-1 are directly related to the severity of metabolic syndrome [13]. The metabolic syndrome explains a major part of plasma PAI-1 level variability, PAI-1, which otherwise behaves as an acute phase reactant, was demonstrated to be independently associated with metabolic syndrome with this relationship being stronger in men than in women (45%versus 26%). Interventional studies reported that if insulin resistance is improved plasma PAI-1 levels decrease. Race seems to have a definite influence on PAI-1.Both genetic and lifestyle factors may contribute to this difference in plasma levels.[19]

Decreased plasma PAI-1 concentrations were observed after weight reduction by a hypo caloric diet and were associated with decreased body fat. In addition treatment with insulin –sensitizing drugs like metformin or troglitazone decrease plasma PAI-1 levels in subjects with type 2 diabetes and to some extent in normal obese subjects[14, 15,16]. Simvastatin in addition to reducing LDL –c it reduces inflammation in MS subjects Simvastatin also reduces circulating plasminogen activator inhibitor-1 activity in volunteers with metabolic syndrome.

The levels of PAI-1, soluble p-selectin and CD40 ligand play an important role in the

development and progression of atherosclerosis; their levels are increased in metabolic syndrome.

Metabolic syndrome has endothelial dysfunction, decreased circulating adiponectin, and high expression of angiogenic inhibitors such as PAI-1[17]

The mechanism of PAI-1overexpression during obesity is complex and it is conceivable that several inducers are involved at the same time at several sites of synthesis. Interestingly, recent in vitro and in vivo studies showed that beside its role in the atherothrombosis PAI-1 is also implicated in adipose tissue development and in the control of insulin signalling in adipocytes. These suggest that PAI-1 inhibitors serve in the control of atherothrombosis and insulin resistance [18]

The link between PAI-1 and metabolic syndrome with obesity was established many years ago. Increased PAI-1level can be now considered a true component of the syndrome [5]

Like our results in which PAI-1 had positive association between components of metabolic syndrome: BMI (p=0.001),waist circumference (p<0.001) systolic blood pressure (p=-0.015) fasting blood sugar (p<0.001),however no association with triglycerides (p=0.133) or HDL (p=0.855)

In a study done by Greyling et al[19] they observed a lack of association of plasma PAI-1 antigen concentrations with parameters of the metabolic syndrome (general and visceral adiposity, blood pressure and lipids in Africans) ,whereas these associations were prominent in Caucasian women. PAI is directly secreted by adipose tissue, especially by plasma concentrations of PAI in obesity Investigations performed on PAI deficient mice[20] and with pharmacological inhibitors of PAI reinforced the notion that the absence of PAI reduces the differentiation of adipocytes and protects against insulin resistance and diet-induced obesity, suggesting a paracrine effect of PAI on promoting of weight gain . This is also in accordance with several population based prospective studies demonstrating that PAI is the only biomarker that predicts incident metabolic syndrome and diabetes.

Metabolic syndrome subjects have raised levels of PAI-1, associated with an increased risk of MI, correlating with obesity[19,21] PAI-1 which otherwise behaves as an acute phase reactant, was demonstrated to be independently associated with metabolic syndrome, even after adjustment with HOMA-IR and other co-variables ,this finding reinforces the results of previous cross-sectional studies that considered haemostatic and inflammatory markers and observed that outstanding relationship between PAI-1 and metabolic syndrome[22]

The association between PAI_{act} and markers of the metabolic syndrome in Caucasians is well established [9, 11]

The results of the study of Bronat etal[22] indicate that HbA1C and PAI are strongly and independently related to metabolic syndrome .Moreover, the elevation of both markers seems to be a manifestation of the same pathophysiological mechanism that underlies the main characteristics of the syndrome.Therfore, PAI-1 and HbA1C should be considered as true components of metabolic syndrome and may be considered as candidates for inclusion in the list of diagnostic criteria.[22]

PAI-1 is also a valuable biomarker for predicting the metabolic syndrome(MS) in elderly residents in study done by Chou YY et al[23] mean age 79.9+/- 4 years .Elderly resident with MS had higher systolic and diastolic blood pressure (p<0.001) and higher HOMA-IR (p<0.001), CRP (p=0.008),and PAI-1 levels (p<0.001) than those without the MS .On multivariate logistic regression analysis , PAI-1was an independent risk factor for the MS. Elderly with higher waist circumferences and higher levels of plasma fasting glucose and TG and lower level HDL had higher PAI-1 levels than those without the above components[23]. Enhancing endogenous fibrinolysis by targeting PAI-1 inhibitor, the primary inhibitor of circulating plasminogen activators, has been shown to be effective in markedly attenuating the formation of arterial and venous occlusive thrombosis in animal models .In addition ,animal and human studies of PAI-1 deficiency indicate that spontaneous bleeding complications associated with even complete PAI-1 deficiency would be rare .Patients most likely to benefit from PAI-1 inhibition would be those at high risk for vascular events, with elevated PAI-1 levels , such as is in obesity ,diabetes and the metabolic syndrome .Since obesity and metabolic syndrome are now epidemic and will likely have a major adverse impact on vascular thrombotic events. It may be time to test the clinical effectiveness of PAI-1 inhibition in those populations at high risk for vascular thrombosis [24].

Sedentary lifestyle is characterized by alterations in pro-inflammatory markers in the plasma [3,4]. Several studies have consistently shown that low levels of plasma high density lipoprotein (HDL) and high levels of low and very low density lipoprotein (LDL and VLDL respectively) are linked with a sedentary life style and are strong predictor to cardiovascular disease [25, 26, 27]

It remains slightly unknown if long term moderate /high intensity exercise have lowered pro-inflammatory and increased anti-inflammatory markers than sedentary subjects.

In our study total cholesterol, LDL,HDL, triglycerides, CRP,PAI-1 levels were lower after moderate intensity exercise in relation to levels before moderate intensity exercise ($p<0.05$).In addition we observed a positive correlation between PAI-1 and LDL after exercise ($r=0.301$, $p=0.053$), PAI and triglycerides after exercise ($r=0.286$, $p=0.066$), negative correlation between HDL and PAI-1 ($r=-0.315$, $p=0.042$).

Our results were similar to Fabio etal[28], Teramoto etal[29], Coen etal[30] these studies detected the favourable effect of exercise on lipid profile and PAI-1.

In a study done by Fabio et al seven male leading sedentary life and seven highly trained athletes subjects were recruited. Blood samples were collected after an overnight fast, plasma lipid profile, glucose, adiponectin, C-reactive protein and PAI-1 levels were determined. Results of the study showed lower plasmatic lipid profile and PAI-1 levels in highly trained athletes ($p=0.01$) than sedentary subjects. In addition the total plasma cholesterol, LDL-c and TG concentration were positively correlated with PAI-1 levels. These results indicate that life style associated with high intensity and high volume exercise induces favourable changes in the lipid profile and PAI-1 levels and may reduce risk of cardiovascular diseases [28]

The effect of Short-term exercise training does not change PAI-1 levels in normal, asymptomatic men and women. In addition, modest decreases in insulin and triglyceride in individuals with elevated body fatness do not result in changes in PAI-1 after short-term training. It appears likely that decreases in PAI-1 with exercise training require decreases in adiposity and/or marked changes in metabolic variables. This was shown In study done by Bodary PF et al[31] they examined the influence of 10 days of moderate-intensity exercise training on measures of fibrinolysis. Sixteen men and 16 women between the ages of 50 and 70 yr were randomly assigned to exercise (EX) and control groups (CON) that were balanced for gender and hormone replacement therapy. Blood samples were collected on days 1, 2, 11, and 12 for measurement of plasma PAI-1, tPA, insulin, glucose, and triglyceride. Subjects in EX performed 50 min of treadmill walking at an intensity corresponding to 65% of heart rate reserve each day for 10 consecutive days.There were no significant changes in PAI-1, tPA, or associated metabolic variables between exercise and Control group during the intervention period. Within Exercise subjects, those with higher body fatness had a significant decrease in insulin and triglyceride compared with those with lower body fatness. However, no changes in fibrinolytic measures were observed within these subgroups. They concluded that Short-term exercise training does not change PAI-1 levels in normal, asymptomatic men and women. In addition, modest decreases in insulin and triglyceride in individuals with elevated body fatness do not result in changes in PAI-1 after short-term training. It appears likely that decreases in PAI-1 with exercise training [31].

6. Conclusion:

Moderate intensity exercise induces favorable changes in metabolic syndrome in lowering lipid profile and PAI-1 levels and may reduce risk of cardiovascular diseases

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