

# Coagulation, fibrinolytic and cytokines parameters response to weight reduction in obese subjects

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## ABSTRACT

**Background:** Obesity is a major risk factor for developing cardiovascular disorders due to increased platelets count and platelets activation.

**Objective:** The aim of this study was to measure the influence of weight loss on the coagulation and fibrinolysis parameters among obese patients.

**Material and Methods:** One hundred obese subjects of both genders (mean age  $46.72 \pm 3.13$  year) selected from the Internal Medicine Department at King Abdul Aziz University Teaching Hospital, their body mass index (BMI) ranged from 32 to 36 Kg/m<sup>2</sup>. Participants enrolled randomly into two study groups; the first group (A) received aerobic exercises and diet regimen for three months, while the second group (B) received no exercise training or diet regimen for three months.

**Results:** Mean values of von Willbrand factor antigen (vWF-Ag), fibrinogen, plasminogen activator inhibitor-1 antigen (PAI-1:Ag) and plasminogen activator inhibitor-1 activity (PAI-1:Ac), tumor necrotic factor-alpha (TNF- $\alpha$ ), Interleukin - 6 (IL-6) and body mass index (BMI), while the mean values of partial thromboplastin time (PTT), prothrombin time (PT), tissue plasminogen activator antigen (tPA:Ag) and tissue plasminogen activator activity (tPA:Ac) increased significantly after 3 months in group (A) as a result of weight reduction program. However, the mean values of all investigated parameters of group (B) had no significant changes. Moreover, comparison between both groups had statistical significant differences in all investigated parameters at the end of the study ( $P < .05$ ).

**Conclusion:** weight reduction program modulates systemic inflammation, fibrinolytic and coagulation of obese subjects.

**Keywords:** obesity, inflammatory cytokines, coagulation, fibrinolytic parameters

## INTRODUCTION

Obesity is a major risk factor for developing cardiovascular disorders due to increased platelets count and platelets activation (1-3), disturbed blood lipid profile, endothelial dysfunction systemic inflammation and atherosclerosis (4, 5). Despite all the improved knowledge on the pathogenesis and treatment of atherothrombosis associated with obesity, it is predicted that coronary heart disease will be the dominant cause of mortality worldwide by 2020 (6).

Obesity is usually associated with reduction of fat tissue oxygenation leads to production of inflammatory cytokines (7) as tumor necrosis factor- $\alpha$ , interleukin-6 (8), leptin and resistin produced because of adipose tissue dysfunction (9). Increased levels of systemic inflammation markers as Interleukin-6 (IL-6) which induces increased platelet count size and function (10), Moreover, increased biomarkers of platelet adhesion and endothelial cell function can be induced by the high level of serum of tumor necrosis factor- alpha (TNF- $\alpha$ ) (11).

Regular exercise training can modulate the coagulation and fibrinolytic parameters (12) because of reduction of body fat tissue, which may reduce the cardiovascular system disorders (CVD) (13-15). In addition, weight reduction can have a great contribution in limitation of morbidity and mortality related to CVD through amelioration of endothelial dysfunction and fibrinolytic abnormalities (16, 17).

The aim of this study was to measure the influence of weight loss on the coagulation and fibrinolysis parameters among obese patients.

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## MATERIALS AND METHODS

### Subjects

One hundred obese subjects of both genders (mean age  $46.72 \pm 3.13$  year) selected from the Internal Medicine Department at King Abdul Aziz University Teaching Hospital, their body mass index (BMI) ranged from 32 to 36 Kg/m<sup>2</sup>. Smoking, hypertension, diabetes, hyperthyroidism, cardiovascular disorders and drugs affecting coagulation were the exclusion criteria. Participants enrolled into two study groups; the first group (A) received aerobic exercises and diet regimen for 12 weeks, the second group (B) received no exercise training or diet regimen for three months. All participants signed the consent form before sharing in the study.

### Methods

#### Equipment

1) Treadmill (Enraf Nonium, Model display panel Standard, NR 1475.801, Holland) used in performance of aerobic walking exercise.

2) Weight and height scale (JENIX DS 102, Dongsang, South Korea) used to measure weight and height to calculate the body mass index (BMI).

#### Measurements

- 1. Laboratory analysis:** An overnight venous blood samples drawn, centrifuged at speed of 3500 RPM for 10 minutes and stored frozen at  $-80^{\circ}\text{C}$  for analysis of plasma Willbrand factor antigen (vWF-Ag), fibrinogen, plasminogen activator inhibitor-1 antigen (PAI-1:Ag), plasminogen activator inhibitor-1 activity (PAI-1:Ac), partial thromboplastin time (PTT), prothrombin time (PT), tissue plasminogen activator antigen (tPA:Ag) and tissue plasminogen activator activity (tPA:Ac) employing the ST-4 coagulation instrument (Zymutest Fibrinogen, ELISA, Hyphen Biomed, Neuville sur Oise, France). Tumor necrotic factor - alpha (TNF-  $\alpha$ ) and Interleukin - 6 (IL-6) levels analyzed with ELISA kits with ELISA microplate strip washer in addition to ELISA microplate reader.
- 2. Evaluation of anthropometric parameters:** Body weight was measured with a calibrated balance scale (HC4211, Cas Korea, South Korea) and the body height was measured using (JENIX DS 102, Dongsang, South Korea), while body mass index (BMI) was determined by equation :  $\text{BMI} = \text{Body weight} / (\text{Height})^2$ . All measurements of BMI, vWF, PT, PTT, PAI-1, TPA, fibrinogen TNF- $\alpha$  and IL-6 were taken before the study (pre-test) and after three months (post-test).

#### Procedures

Following the previous evaluation, all participants were randomly included into two study groups:

- 1. Study group (A):** Participants practiced treadmill aerobic exercise training. Training program included five minutes for warming-up in the form of range motion and stretching exercises, 30 minutes of aerobic exercise training with intensity equal 60-70% of the individual maximum heart rate followed by cooling down for 10 minutes ( on treadmill with low speed and without inclination). Participants had 3 sessions /week for 3 months with close supervision of physical therapist. In addition, a dietitian performed an interview-based food survey for all participants of group (A) for detection of feeding habits, abnormal dietary behavior and to prescribe the balanced low caloric diet that provided 1200 Kilocalories/day for 12 weeks. The same dietitian continuously monitored all participant caloric intake through reviewing the detailed record of food intake every 2 weeks by the dietitian.
- 2. Group (B):** Participants only received no exercise training or diet regimen for 3 months.

#### Statistical analysis

Mean values of the investigated parameters compared by student paired "t" test. While, the unpaired" test used to compare between the two groups ( $P < 0.05$ ).

## RESULTS

Detailed baseline characteristics of all participants presented in **Table 1**. There was no significant difference for all characteristics in both groups (**Table 1**).

**Table 1: Characteristics of all participants**

	Group (A) (no=50)	Group(B) (no=50)	Significance
Age (year)	45.38 ± 2.91	46.82 ± 3.65	P>0.05
Gender (male/female)	22/18	23/17	P>0.05
BMI (kg/m <sup>2</sup> )	34.57 ± 2.34	35.12 ± 2.36	P>0.05
Neck circumference (cm)	40.98 ± 3.11	42.15 ± 3.46	P>0.05
Waist circumference (cm)	108.35 ± 9.23	110.27 ± 8.95	P>0.05
Waist-to-hip ratio	0.82 ± 0.06	0.91 ± 0.07	P>0.05
SBP (mmHg)	130.24 ± 10.13	132.35 ± 11.59	P>0.05
DBP (mmHg)	85.16 ± 4.92	86.72 ± 5.31	P>0.05

BMI: Body Mass Index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

**Table 2: Mean value and significance of PT, BMI, PTT, tPA:Ag, tPA:Ac, vWF-Ag, fibrinogen, PAI-1:Ag, PAI-1:Ac, TNF-α and IL-6 in group (A) before and at the end of the study**

	Mean ± SD		t- value	Significance
	Before	After		
BMI (Kg / m <sup>2</sup> )	34.57 ± 2.34	26.92 ± 5.43*	8.21	P < 0.05
PTT (s)	20.53 ± 3.46	24.72 ± 3.38*	6.17	P < 0.05
PT (s)	10.62 ± 1.74	12.81 ± 1.65*	5.36	P < 0.05
Fibrinogen (mg/mL)	3.91 ± 0.83	2.41 ± 0.82*	4.23	P < 0.05
tPA:Ac (IU/mL)	5.27 ± 0.94	6.83 ± 0.86*	4.75	P < 0.05
tPA:Ag (ng/mL)	3.13 ± 0.72	4.82 ± 0.68*	4.31	P < 0.05
vWF-Ag (%)	91.26 ± 11.27	72.82 ± 10.88*	9.18	P < 0.05
PAI-1:Ag (ng/mL)	18.26 ± 3.91	10.12 ± 3.78*	5.42	P < 0.05
PAI-1:Ac (AU/mL)	4.73 ± 0.86	3.24 ± 0.75*	4.63	P < 0.05
IL-6 (pg/mL)	8.51 ± 2.16	5.75 ± 1.98*	5.22	P < 0.05
TNF- α (pg/mL)	5.43 ± 1.43	4.11 ± 1.25*	4.63	P < 0.05

BMI: Body Mass Index; PT: prothrombin time; PTT: partial thromboplastin time; tPA:Ac: tissue plasminogen activator activity; tPA:Ag: tissue plasminogen activator antigen; vWF-Ag: von Willbrand factor antigen; PAI-1:Ac: plasminogen activator inhibitor-1 activity; PAI-1:Ag: plasminogen activator inhibitor-1 antigen; TNF-α: tumor necrotic factor - alpha; IL-6: Interleukin-6; (\*): indicates a significant difference, P < 0.05

**Table 3: Mean value and significance of PT, BMI, PTT, tPA:Ag, tPA:Ac, vWF-Ag, fibrinogen, PAI-1:Ag, PAI-1:Ac, TNF-α and IL-6 in group (B) before and at the end of the study**

	Mean ± SD		t- value	Significance
	Before	After		
BMI (Kg / m <sup>2</sup> )	35.12 ± 2.36	34.28 ± 5.47	1.12	P>0.05
PTT (s)	20.82 ± 3.21	21.12 ± 3.20	0.74	P>0.05
PT (s)	11.15 ± 1.82	11.63 ± 1.85	0.81	P>0.05
Fibrinogen (mg/mL)	3.88 ± 0.84	3.79 ± 0.81	0.64	P>0.05
tPA:Ac (IU/mL)	5.62 ± 0.74	5.48 ± 0.69	0.68	P>0.05
tPA:Ag (ng/mL)	3.22 ± 0.59	3.17 ± 0.53	0.79	P>0.05
vWF-Ag (%)	92.15 ± 11.23	90.14 ± 11.18	1.25	P>0.05
PAI-1:Ag (ng/mL)	18.74 ± 3.81	18.16 ± 3.42	0.51	P>0.05
PAI-1:Ac (AU/mL)	4.83 ± 0.91	4.75 ± 0.86	0.66	P>0.05
IL-6 (pg/mL)	8.32 ± 2.24	8.18 ± 2.21	0.62	P>0.05
TNF- α (pg/mL)	5.49 ± 1.37	5.31 ± 1.35	0.65	P>0.05

BMI: Body Mass Index; PT: prothrombin time; PTT: partial thromboplastin time; tPA:Ac: tissue plasminogen activator activity; tPA:Ag: tissue plasminogen activator antigen; vWF-Ag: von Willbrand factor antigen; PAI-1:Ac: plasminogen activator inhibitor-1 activity; PAI-1:Ag: plasminogen activator inhibitor-1 antigen; TNF-α: tumor necrotic factor - alpha; IL-6: Interleukin-6

Mean values of von Willbrand factor antigen (vWF-Ag), fibrinogen, plasminogen activator inhibitor-1 antigen (PAI-1:Ag) and plasminogen activator inhibitor-1 activity (PAI-1:Ac), tumor necrotic factor - alpha (TNF-α), Interleukin-6 (IL-6) and body mass index (BMI), while the mean values of partial thromboplastin time (PTT), prothrombin time (PT), tissue plasminogen activator antigen (tPA:Ag) and tissue plasminogen activator activity (tPA:Ac) increased significantly in group (A) after 3 months of the weight reduction program. However, the mean values of all investigated parameters of group (B) had no significant changes (Table 2 and 3). Moreover, comparison between both groups had statistical significant differences in all investigated parameters at the end of the study (Table 4) (P<.05).

**Table 4:** Mean value and significance of PT, BMI, PTT, tPA:Ag, tPA:Ac, vWF-Ag, fibrinogen, PAI-1:Ag, PAI-1:Ac, TNF- $\alpha$  and IL-6 in group (A) and group (B) at the end of the study

	Mean $\pm$ SD		t- value	Significance
	Group (A)	Group (B)		
BMI (Kg / m <sup>2</sup> )	26.92 $\pm$ 5.43	34.28 $\pm$ 5.47*	6.23	P < 0.05
PTT (s)	24.72 $\pm$ 3.38	21.12 $\pm$ 3.20*	4.82	P < 0.05
PT (s)	12.81 $\pm$ 1.65	11.63 $\pm$ 1.85*	4.21	P < 0.05
Fibrinogen (mg/mL)	2.41 $\pm$ 0.82	3.79 $\pm$ 0.81*	3.72	P < 0.05
tPA:Ac (IU/mL)	6.83 $\pm$ 0.86	5.48 $\pm$ 0.69*	3.64	P < 0.05
tPA:Ag (ng/mL)	4.82 $\pm$ 0.68	3.17 $\pm$ 0.53*	3.51	P < 0.05
vWF-Ag (%)	72.82 $\pm$ 10.88	90.14 $\pm$ 11.18*	7.33	P < 0.05
PAI-1:Ag (ng/mL)	10.12 $\pm$ 3.78	18.16 $\pm$ 3.42*	4.22	P < 0.05
PAI-1:Ac (AU/mL)	3.24 $\pm$ 0.75	4.75 $\pm$ 0.86*	3.61	P < 0.05
IL-6 (pg/mL)	5.75 $\pm$ 1.98	8.18 $\pm$ 2.21*	4.23	P < 0.05
TNF- $\alpha$ (pg/mL)	4.11 $\pm$ 1.25	5.31 $\pm$ 1.35*	4.16	P < 0.05

BMI: Body Mass Index; PT: prothrombin time; PTT: partial thromboplastin time; tPA:Ac: tissue plasminogen activator activity; tPA:Ag: tissue plasminogen activator antigen; vWF-Ag: von Willbrand factor antigen; PAI-1:Ac: plasminogen activator inhibitor-1 activity; PAI-1:Ag: plasminogen activator inhibitor-1 antigen; TNF- $\alpha$ : tumor necrotic factor - alpha; IL-6: Interleukin- 6; (\*): indicates a significant difference, P < 0.05

## DISCUSSION

As disorders of coagulation and fibrinolysis have a great contribution in obesity related cardiovascular disorders (18, 19). We found that weight loss program improves the parameters of systemic inflammation along with amelioration of coagulation disorders in obese subjects, our findings were in line with many previous studies. *Barbeau and colleagues* stated that weight loss could reduce the cardiovascular disorders (CVD) mortality rate via modulation of endothelial and fibrinolytic dysfunction (20). *Svensen and colleagues* proved that weight reduction could control oxidative stress, platelets activation and chronic inflammation in obese women (21). In addition, *Anfossi and colleagues* found that 10% body weight loss is able to correct platelet abnormalities related to central obesity related insulin resistance (1).

Concerning PAI-1 activity & antigen and tPA activity & tPA antigen our results showed that weight loss significantly increase the values of tPA antigen and tPA activity and reduce the values of PAI-1 activity and antigen, these findings are in line with many previous trials of weight loss (20-22). In addition, *Murakami and colleagues* stated that increased values of PAI-1 activity positively correlated with high values of BMI in obese subjects, which reduced as a result to weight loss [13]. However, regarding PTT, PT and vWF-Ag, our results revealed an increase in the mean values of PTT and PT because of weight loss and these findings agreed with *Piccone et al.* (23) and *Stratton et al.* concluded that a six months of endurance exercises resulted in reduction in fibrinogen and PAI-1 activity and enhanced the t-PA activity in elderly men (24). However, there was a significant reduction of vWF and these results are in line with *Saenko et al.* (25) and *Paton et al.* stated that serum vWf:Ag and tPA antigen were reduced in ten subjects performed two maximal oxygen uptake (VO<sub>2</sub>max) test trials (26).

Concerning our results regarding the serum level fibrinogen, weight loss led to reduction in fibrinogen concentration, this finding is in line with *DeSouza et al.* proved that physically active postmenopausal women have lower serum fibrinogen, t-PA antigen, PAI-1 antigen, and PAI-1 activity and higher (P<.01) t-PA activity levels than sedentary postmenopausal women (27), which may be due to reduced body fat mass as a result of regular exercises (28, 29). Moreover, results of this study indicated a great significant reduction in TNF- $\alpha$ , IL6 and BMI only in-group (A) this means that weight reduction is an effective anti-inflammatory treatment, these results agreed with *Esposito et al.* proved that weight reduction led to reduction in inflammatory cytokines and increase the serum levels of anti-inflammatory cytokines in obese women (30). *Reinher and colleagues* clearly stated that life style modification program reduces serum level of TNF- $\alpha$  (31). In addition, *Gallistat et al.* stated that a three weeks weight-reducing program resulted in significant decrease in IL-6, body fat mass and BMI (32).

## CONCLUSION

Weight reduction program modulates systemic inflammation, fibrinolytic and coagulation of obese subjects.

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