

Leptin Level and Plasma Prothrombotic Factors in Obese Subjects

(¹) **Hamdia Ezzat**, (²) **Eman M Abd El-Rahman**,
(²) **Sabilah G Mousa**, and (³) **Eman A Mahmoud**

(¹)Clinical Pathology & (²)Internal Medicine and (³) Rheumatology & Rehabilitation Departments, Al-Azhar and Assiut University

Abstract:

Obesity is associated with increased cardiovascular morbidity and mortality. Abnormalities in coagulation and haemostasis represent a well-known link between obesity and thrombosis (both arterial and venous).

In human, production of a depocyte-derived peptide, leptin has been linked to adiposity; recent studies have shown that plasminogen activator inhibitor-1 (PAI-1), a prothrombotic factor associated with atherosclerosis complication is also produced in adipose tissue.

Several studies reported that obese subjects had elevated levels of vonWillbrand factor (vWF) and fibrinogen .

The aim of this work is to examine the relationship of obesity, fat distribution and serum leptin concentration with plasma levels of Prothrombotic factors (PAI-1 – (vWF) and fibrinogen) and lipid pattern (Triglycerides and Cholesterol) as metabolic parameters. The body fat distribution was evaluated by measuring the body mass index (BMI) and waist-to-hip ratio (WHR).

This study was carried out on four groups:

Group I (Control Group): Which is subdivided into two groups:

Group Ia: Consists of 10 apparently healthy normal females with BMI ≤ 25 kg/m².

Group Ib: Consists of 10 apparently healthy normal males with BMI ≤ 25 kg/m².

Group II (Female Obese): 16 obese females with BMI ≥ 30 kg/m².

Group III (Male Obese): 16 Obese males with BMI ≥ 30 kg/m².

Results can be summarized as follows:

1. Very highly significant increase in serum leptin levels in group II and III vs group I (P<0.0001). Serum leptin was increased non-significantly in female group than male group (P> 0.05).
2. Highly significant increase in serum concentration of cholesterol and triglycerides levels in group II and III vs group I.
3. Obese subjects (group II and group III) had higher plasma concentration of all prothrombotic factors as compared to lean groups (GI) . PAI-1 P< 0.0001 for both obese groups, vWF and fibrinogen, P< 0.001 for both obese groups.
4. Significant increase in plasma levels of both PAI-1 and fibrinogen in female obese as compared to male obese (P < 0.05). Plasma level of vWF was increased non-significantly in female obese than male obese (P > 0.05).

There was significant positive correlation between BMI and WHR, also there was a significant positive correlation between both of them and serum leptin concentration, plasma PAI-1, vWF and fibrinogen in groups II and group III.

- WHR are positively associated with serum cholesterol and triglycerides in group II and group III.
- There was significant positive correlation between leptin concentration and plasma PAI-1, vWF, fibrinogen, cholesterol and triglycerides in both obese groups.

Leptin Level and Plasma Prothrombotic.....

- There was significant positive correlation between PAI-1 and vWF, also there was significant positive correlation between both of them and fibrinogen in group II and group III.
- There was significant positive correlation between serum triglycerides and PAI-1 in both obese groups.

In conclusion: Increased body fat mainly (abdominal fat) are associated with increased concentrations of cardiovascular risk factors. Plasma concentration of the prothrombotic factors are increased in obese subjects as compared to non-obese controls, leptin seems to be involved in this elevation and emerges as a predictor of circulating PAI-1, vWF and fibrinogen concentration. Increased PAI-1 expression in obese subjects can directly influence vessel wall remodeling and play an important role in the development of atherosclerosis by decreasing fibrin degradation.

Introduction

Obesity is associated with increased cardiovascular morbidity and mortality (Pascual *et al.*, 2003 and Lowenstein *et al.*, 2004). Adipocytes are the sites where triglycerides are stored or free fatty acids are released, depending on the body's energy demands (Cianflone *et al.*, 1995). In addition, adipocytes produce several mediators; one of them is leptin, the product of the obese gene that might regulate body weight signaling the amount of body fat (Maffei *et al.*, 1995).

Recently, production of PAI-1 by adipose tissue, in particular by fat from omentum have evidenced and it has been proposed that it could be responsible for the elevated plasma PAI-1 level observed in insulin resistance Diabetes (Juhan-Vague *et al.*, and 2000 Mavri *et al.*, 2001). This tissue also produces several effector molecules that can up regulate PAI-1. these molecules include transforming growth factor beta, tumor necrosis factor alpha, angiotensin II and interleukin-6, all of which up regulate PAI-1 in various cell types (Mutch *et al.*, 2001).

Obese patients have higher plasma concentrations of all prothrombotic factors (fibrinogen, vWF and factor VII) as compared to non-obese control with a positive association with central fat (De Pergola *et al.*, 2002). Furthermore, obesity is characterized by higher plasma concentration of antithrombotic factors such as tissue type plasminogen activator (t-PA) and protein C, as compared to non-obese controls, the increase in these factors

being likely to represent a protective response counteracting the increase in prothrombotic factors (De Pergola *et al.*, 1997).

The aim of this work is to determine the relationship of obesity, fat distribution, serum leptin concentration with the plasma levels of prothrombotic factors (PAI-1, vWF and Fibrinogen) and lipid pattern (triglycerides and cholesterol) as metabolic parameters.

Patients & Methods

The present work was carried out on 52 subjects. They were divided into four groups:

Group I : Consisted of 20 apparently healthy normotensive, non-smoker and non-diabetic hospital workers or their relatives. This group was further subdivided into:

Group Ia: Consist of 10 normal healthy lean females with an age ranged from 25-43 years (mean 35 years) and their BMI ranged from 20.7-25 with mean of $23.1 \text{ kg/m}^2 \pm 2$ and WHR ranged from 0.70 - 0.85 with a mean of 0.8 ± 0.05 .

Group Ib: Consisted of 10 normal healthy lean males with an age ranged from 24-44 years (mean 36 years) and their BMI ranged from 22-25 with mean of $24.5 \text{ kg/m}^2 \pm 1.3$ and WHR ranged from 0.8 - 0.94 with a mean of 0.89 ± 0.1 .

Group II: Consisted of 16 obese females with an age ranged from 26-40 years (mean

of 34 years) and their BMI ranged from 30.1 - 36.8 with a mean of $33.4 \text{ kg/m}^2 \pm 1.78$ and WHR ranged from 0.9-1.2 with a mean of 1.05 ± 0.1 .

Group III: Consisted of 16 obese male with age ranged from 27-42 years (mean 35.5 years) and their BMI ranged from 31.5 -37.7 kg/m^2 with a mean of $35.7 \text{ kg/m}^2 \pm 2.4$ and WHR ranged from 0.99-1.2 with a mean of 1.19 ± 0.109 .

All of the studied subjects were none diabetic normotensive, none had cardiovascular complications or any previous history of pulmonary disease non suffering from any chronic or acute disease, none taking any drug that could affect the coagulation test. None of the females was receiving oral contraceptives and pregnant females were excluded. Smoker and subjects with endocrine disease were excluded.

All the 52 persons were subjected to the following:

- i. Detailed physical examination to exclude endocrine and cardiac comorbidities.
- ii. **BMI Calculation:** Height and weight were measured and the BMI were calculated by a simple mathematical equation by dividing weight (kg)/height² (m²). The normal range of BMI (19.1-25 kg/m^2) (Karl and Hymnsfield, 1987).
- iii. **WHR Calculation:** The waist circumference and hip circumference was measured at the level of umbilicus "minimal waist girth" and the symphysis pubis (maximal hip girth) respectively. Then the waist/hip ratio was calculated by dividing the waist circumference/hip circumference (Karl and Hymnsfield, 1987).
- iv. **Laboratory Investigation:** From each subject 10 ml blood were collected, blood was divided as follows:
 1. Two ml were collected into tube containing dipotassium EDTA, used for complete blood count by (fully automated blood counter "Coulter T660").
 2. Four ml were collected into a plain tube, and allowed to clot .Serum was

divided into 3 aliquots, one tube were stored at -20°C for measurement of serum leptin, and the other two tubes were ready for:

- a. Routine chemistry tests: Kidney function tests (serum creatinine and urea), liver function tests (AST, ALT, T.Bil & ALP),and fasting blood glucose were determined using fully automated chemistry analyzer (Hitachi 911) to exclude other systemic disease.
- b. Lipid profile included serum levels of total cholesterol (TC),and triglycerides (TG) were performed using commercial kits from Boehringer Mannheim.

Measurments of serum leptin (Akira *et al.*, 1997):

Serum leptin was measured by using enzyme linked immunosorbent assay, (ELISA) kit, supplied from diagnostic system laboratories Inc (DSL). The assay is based on an oligoclonal system in which a blend of monoclonal antibodies (MAbs) directed against human leptin are used.

Standard or sample containing serum leptin react with capture monoclonal antibodies (antihuman leptin antibody) coated on the microtitre well, after incubation and washing the wells were treated with antibody enzyme conjugate solution (antihuman leptin detection antibody labeled with horseradish peroxidase "HRP").

After an incubation period allowing the formation of a sandwich, the microtiter plate is washed to remove unbound enzyme labeled antibodies. Then the well were incubated with substrate tetramethyle benzidine (TMB) for 10 minutes.

An acidic stopping solution was then added and the amount of enzymatic turnover is determined colourmetrically by measuring the absorbance which is proportional to serum leptin concentration in the sample.

3. We added 3.6 ml of blood to 0.4 ml of trisodium citrate (3.8%), mixed well and kept on Ice until centrifuged. The sample was centrifuged for 15 minutes at 3000 g and at temperature of 4°C to prepare platelet poor plasma with

Leptin Level and Plasma Prothrombotic.....

minimal platelet activation for the estimation of prothrombotic factors.

- a. Fibrinogen was done immediately by using fully automated coagulation analyzer (sysmex dade Behring coagulation analyser).

The rest of the plasma was kept in 2 Eppendorph plastic tubes and stored immediately at -20°C for a period not more than one month (until all blood sample were collected) and was used later for estimation of both PAI-1 and vWF.

Measurement of plasminogen activator inhibitor-1 (PAI-1) (Booth et al., 1988):

Immunobind plasma PAI-1 ELISA kit from American diagnostic, USA is a commercial ELISA kit used for quantitative determination of human PAI-1 antigen based on sandwich technique.

Measurement of von Willebrand factor by READs, (Corgenis, Inc.) (Blann and McCllum, 1994):

READs vWF Ag assay is a sandwich ELISA.

Statistical Analysis:

All values were statistically analyzed through IBM computer using CSS/PC; Basic state, descriptive statistics. Such as means and standard deviation were used for numerical variables.

Comparison of the value was performed using paired student's T-test and the two tailed P-value.

Regression analysis was performed to evaluate the correlation among the different parameters using spearman correlation coefficient (r). P is considered significant when it is < 0.05) (Sendecor and Cochran, 1968).

Results:

Table (1) shows that, obese subjects group II and group III had a highly significant elevation in weight, BMI, and

WHR as compared to normal control groups (group Ia & group Ib).

Table (2) shows that, there is highly significant increase in serum cholesterol and triglyceride levels in group II and group III as compared to normal lean subjects. No significant difference were noted in the level of cholesterol or triglyceride when compared female obese to male obese.

Serum leptin was significantly very high in obese subjects as compared to lean subjects. Serum leptin was increased non-significantly in group II as compared to group III.

Plasma PAI-1, vWF Ag and fibrinogen were significantly very high in obese subjects (group II & group III) when compared to lean subjects (group Ia & group Ib).

There were significant increase in PAI-1 and fibrinogen levels when compared group II (female obese) to group III (male obese).

Non-significant increase in vWF Ag was noticed in obese female as compared to obese male.

Tables (3 & 4) show that there were a significant positive correlation between BMI and WHR in group II and group III. Also, there was a significant positive correlation between both of them and serum leptin concentration, plasma PAI-1, vWF Ag and fibrinogen in group II and group III. WHR was positively correlated with serum cholesterol and triglycerides in female and male obese.

There was no correlation between BMI and cholesterol or triglycerides in obese groups.

Tables (5 & 6) show that serum leptin concentration was positively correlated with plasma levels of PAI-1, vWF, fibrinogen cholesterol and triglycerides in both obese group.

Plasma PAI-1 level was positively correlated with vWF, fibrinogen and triglycerides in both obese group.

Positive correlation was found between plasma vWF and fibrinogen in both obese group.

Table (1): Statistical comparison (mean ± SD) of weight, height, BMI and WHR in different studied groups.

Variables	♀ control Group Ia (n = 10)	♂ control Group Ib (n = 10)	♀ Obese Group II (n = 16)	♂ Obese Group III (n = 16)	Group II vs Group Ia	Group III vs Group Ib	Group II vs Group III
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	P-value	P-value	P-value
Weight (kg)	62.6 ± 4	72 ± 6.5	82.3.6 ± 7.4	97.8 ± 10.2	< 0.001	< 0.001	< 0.01
Height (meter)	1.52 ± 0.04	1.68 ± 0.09	1.56 ± 0.05	1.65 ± 0.058	> 0.05	> 0.05	< 0.01
BMI (kg/m ²)	23.1 ± 2	24.5 ± 1.3	33.4 ± 1.78	35.7 ± 2.4	< 0.0001	< 0.0001	< 0.05
Waist/hip ratio	0.8 ± 0.05	0.89 ± 0.1	1.05 ± 0.1	1.19 ± 0.1	< 0.0001	< 0.0001	> 0.05

P > 0.05: Insignificant.

P < 0.001: Highly significant.

P < 0.05 : Significant.

P < 0.0001 : Very highly significant.

Table (2): Statistical comparison (mean ± SD) of laboratory data in different studied groups.

Variables	♀ control Group Ia (n = 10)	♂ control Group Ib (n = 10)	♀ Obese Group II (n = 16)	♂ Obese Group III (n = 16)	Group II vs Group Ia	Group III vs Group Ib	Group II vs Group III
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	P-value	P-value	P-value
Cholesterol (mg/dL)	175 ± 13.2	178 ± 15.5	245.9 ± 46	249 ± 37.8	< 0.001	< 0.001	> 0.05
Triglycerides (mg/dL)	110 ± 20	113 ± 18	170.8 ± 12.1	170.3 ± 14	< 0.001	< 0.001	> 0.05
Leptin (ng/mL)	8.37 ± 2.5	7.9 ± 2.1	29.5 ± 4.9	27.3 ± 5.1	< 0.0001	< 0.0001	> 0.05
PAI-1 (ng/mL)	27.9 ± 8.2	24.5 ± 7.9	59 ± 12.8	50.4 ± 6.9	< 0.0001	< 0.0001	> 0.05
vWF Ag (ng/mL)	105 ± 11.5	98 ± 12.3	144 ± 19.2	137.8 ± 12	< 0.001	< 0.001	< 0.05
Fibrinogen (mg/dL)	210 ± 21.3	203 ± 22	324 ± 74.3	282 ± 38.6	< 0.001	< 0.001	< 0.05

P > 0.05: Insignificant.

P < 0.001: Highly significant.

P < 0.05 : Significant.

P < 0.0001 : Very highly significant.

Table (3): Correlation between WHR and BMI with different laboratory parameter in obese female (group II).

	WHR	BMI
	R	R
BMI	0.351	---
Leptin	0.61	0.513
PAI-1	0.622	0.532
vWF	0.709	0.573
Fibrinogen	0.335	0.325
Cholesterol	0.332	0.148
Triglycerides	0.41	0.04

P* ≤ 0.05

Leptin Level and Plasma Prothrombotic.....

Table (4): Correlation between WHR and BMI with different laboratory parameter in obese male (group III).

	WHR	BMI
	R	R
BMI	0.392	---
Leptin	0.81	0.63
PAI-1	0.68	0.378
vWF	0.336	0.31
Fibrinogen	0.365	0.549
Cholesterol	0.35	0.258
Triglycerides	0.47	0.02

Table (5): Correlation between different laboratory parameters in obese female (group II).

	Leptin vs	PAI-1 vs	vWF vs	Fibrinogen vs	Cholesterol vs
	R	R	R	R	R
PAI-1	0.825				
vWF	0.829	0.87			
Fibrinogen	0.554	0.637	0.404		
Cholesterol	0.324	0.207	0.249	0.207	
Triglycerides	0.325	0.339	0.03	0.01	0.03

P* significant if ≤ 0.05

Table (6): Correlation between different laboratory parameters in obese male (group III).

	Leptin vs	PAI-1 vs	vWF vs	Fibrinogen vs	Cholesterol vs
	R	R	R	R	R
PAI-1	0.732				
vWF	0.399	0.87			
Fibrinogen	0.562	0.637	0.361		
Cholesterol	0.351	0.184	0.09	0.247	
Triglycerides	0.338	0.392	0.179	0.047	0.368

P* significant if ≤ 0.05

Discussion:

Obesity is the most common and costly nutritional problem affecting approximately 33% of adults (Kuczmarski *et al.*, 1994). A body mass index greater than 28 is associated with a risk of morbidity. Such as stroke, ischemia, heart disease or diabetes mellitus, that is four times the risk in the general population (Naveau *et al.*, 1997 and Poirier & Despres, 2003).

In this study there was very highly significant increase in serum leptin levels in obese subjects ($P < 0.0001$) for both female and male groups as compared to the control groups. Serum leptin was increased non-significantly in female obese than male obese ($P > 0.05$). Also, there were non-significant increase in serum leptin in

female control group as compared to male control group.

These results are in agreement with that of Liuzzi *et al.*, (1999); Soderberg *et al.* (1999) and Miller *et al.* (2001). This is because leptin impairs several metabolic effects on insulin as stimulation of glucose transport, glycogen synthesis, lipogenesis and protein kinase A activation as well as stimulation of protein synthesis. At low leptin concentrations, insulin sensitivity is increased. At higher concentration, the insulin responsiveness is diminished resulting in nearly complete inhibition of its effect at high leptin level. Thus leptin may be related to the pathophysiology of insulin resistance in both NIDDM and obesity (Hanque and Rahman, 2003).

Porreca *et al.* (2004) agreed with us that obese women had higher levels of leptin than healthy control. They also reported that obesity is associated with enhanced levels of atherosclerosis markers. These abnormalities are related to abdominal obesity possibly mediated by leptin levels and are reversible with weight loss.

Leptin concentrations showed a direct correlation with BMI in both sexes. These results are in agreement with that of Liuzzi *et al.* (1999) and Soderber *et al.* (1999). Leptin concentration showed a direct correlation with WHR. These results disagree with that of Liuzzi *et al.*, (1999) who reported inverse correlation between leptin and WHR.

In this work, there was a significant increase in plasma PAI-1 levels in obese female and male groups as compared to normal control groups. These results were in agreement with that of Mavri *et al.*, (2001) and Romano *et al.* (2003). Mavri *et al.* (2001) reported that only abdominal but not femoral subcutaneous fat were associated with increased in plasma PAI-1 in obese male and female.

In the present study, there was a significant positive correlation between PAI-1 and WHR in both obese group while Kockx *et al.* (1999) reported a relationship between visceral fat and PAI-1 in obese men but not in obese women.

In present study, plasma PAI-1 was associated with serum leptin; this results was in agreement with that of Sudi *et al.* (2000). They also, reported that adiposity and other variables contribute to higher levels of PAI-1. Leptin seems to be, independently linked with fibrinolytic parameters, the unfavorable metabolic and fibrinolytic risk profile might emanate from the obese pubertal stage.

In the present study, there was a significant positive correlation between PAI-1 and triglycerides. These results were in agreement with that of Sundell *et al.* (1988).

Our results showed that (vWF) were elevated in obese women and obese men; as compared to control groups (group Ia & group Ib). Weyer *et al.* (2002) agreed with us, adding that obesity and insulin resistance

appear to be associated with low-grade inflammation and endothelial dysfunction.

Guagnono *et al.* (2003) agreed with us in that obese women had significantly higher levels of leptin and vWF compared to healthy women. They also agreed with our results which showed that leptin were associated with vWF. They reported that leptin, might be a link between obesity and increased morbidity for cardiovascular disease. Leptin exerts proinflammatory, pro-angiogenic actions by activating a specific receptor (ob-Rb) which is expressed in human endothelial cells. Thus, a link may exist between leptin expression and endothelial dysfunction.

In the present work there was a significant increase in plasma fibrinogen levels in obese female and male groups as compared to normal control groups. These results were in agreement with that of De Pergola *et al.* (1997) and Gomez *et al.* (2002).

In this work fibrinogen was associated with BMI and WHR, and there was a strong positive correlation between fibrinogen and serum leptin. This results were in agreement with Comez *et al.* (2002).

Conclusion

Increased body fat mainly (abdominal fat) is associated with increased concentrations of cardiovascular risk factors. Plasma concentration of the prothrombotic factors are increased in obese subjects, as compared to non-obese controls, leptin seemed to be involved in this elevation and emerged as a predictor of circulating PAI-1, vWF and fibrinogen concentration. Increased PAI-1 expression in obese subjects can direct influence vessel wall remodeling and play an important role in the development of atherosclerosis by decreasing fibrin degradation.

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Leptin Level and Plasma Prothrombotic.....

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مستوى اللبتين والعوامل المحفزة على التخثر في الأشخاص المصابين بالسمنة

د. حمدية عزت أحمد⁽¹⁾ ، د. إيمان محمد عبد الرحمن⁽²⁾ ،
د. سبيله جمعه موسى⁽²⁾ ، د. إيمان عباس محمود⁽³⁾
قسم الباثولوجيا الإكلينيكية⁽¹⁾ ، قسم الأمراض الباطنة العامة⁽²⁾ ، قسم الروماتيزم
والتأهيل⁽³⁾ كلية الطب – جامعة الأزهر وجامعة أسيوط .

تعتبر السمنة من أكثر المشاكل الغذائية في العالم التي تصيب حوالي 33% من البالغين وترتبط السمنة بمخاطر صحية كبيرة مثل السكتة الدماغية والإصابة بأمراض القلب الشريانية والبول السكري.

تهدف هذه الدراسة إلى قياس مستوى اللبتين والعوامل المحفزة على التخثر ، وهي: (1) مستوى (ب-أ-1) ، وهو عامل مهبط لمنشط البلازمينوجين-1 ، وقياس عامل فون فولبيراند ، وقياس الفيبرينوجين ودراسة علاقتهم مع السمنة ونسبة الدهون بالجسم لدى الأشخاص المصابين بالسمنة .

وقد تم اختيار 4 مجموعات للانضمام لهذه الدراسة :

المجموعة الأولى: وتقسم إلى مجموعتين وهي مجموعة الرجال والنساء الأصحاء (المجموعتان الضابطتان).

المجموعة الثانية: وهي مجموعة من السيدات البدينات.

المجموعة الثالثة: وهي مجموعة من الرجال المصابين بالسمنة.

وقد أظهرت النتائج زيادة ذات دلالة إحصائية في مستوى اللبتين و (ب-أ-1) عامل مهبط لمنشط البلازمينوجين ، وعامل فون فولبيراند ، وكذلك نسبة الفيبرينوجين في الأشخاص المصابين بالسمنة مقارنة بالأصحاء .

وأيضا أثبتت النتائج وجود دلالة ذات دلالة إحصائية عند مقارنة السيدات البدينات بالرجال المصابين بالسمنة في مستوى الفيبرينوجين و (ب-أ-1) .

وأيضا أثبتت النتائج وجود علاقة إيجابية بين مستوى اللبتين وكلاً من (ب-أ-1) والفيبرينوجين وعامل فون فولبيراند. وكذا وجود علاقة إيجابية بين اللبتين والكوليسترول والدهون الثلاثية.