Thrombosis Research 180 (2019) 110–114

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Differences between metabolically healthy and unhealthy obesity in PAI-1 level
Fibrinolysis, body size phenotypes and metabolism

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ARTICLE INFO

Keywords:
Plasminogen activator inhibitor-1
Thrombosis
Obesity
Fibrinolysis

ABSTRACT

Background: Different studies have recognized the existence of subtypes of obesity and normal weight, in which it is reported that not all patients show the same cardiometabolic risk, called "metabolically healthy" and "metabolically unhealthy". In several reviews, differences in the inflammatory profile have been studied, but there is not information on the relationship of body size phenotypes with thrombosis risk.
Objective: Determine the association between body size phenotypes and fibrinolytic activity by measuring the concentration of plasminogen activator inhibitor-1 (PAI-1).
Methods: A cross-sectional study was conducted in women aged 40 to 65 years. Anthropometric measurements and biochemical determinations were performed on all participants. The fibrinolytic activity was determined by measuring PAI-1 by ELISA. Karelis criteria were used to define metabolic status. Four groups were formed: Metabolically healthy normal weight (MHNW), Metabolically unhealthy normal weight (MUNW), Metabolically healthy obese (MHO) and Metabolically unhealthy obese (MUO).
Results: 230 women were included in our study with a mean age 52.3 ± 5.9 years. The concentration of PAI-1 showed a significant difference between the groups MHNW, MUNW, MHO, MUO [2.3 (0.08, 13.6), 12.7, (0.08, 33.1), 23.4 (2.6, 28.8) and 22.8 (2.0, 46.7) ng/mL, respectively, $p = 0.006$]. Multiple regression analysis identified that BMI and HOMA-IR were independent factors influencing PAI-1 levels.
Conclusion: This study is the first one that recognizes differences in the fibrinolytic activity between body size phenotypes. The groups with the lowest fibrinolytic activity were MUO and MHO, however, MUNW also present alterations of fibrinolysis, thus suggesting a prothrombotic state.

1. Introduction

Obesity affects > 650 million people in the world, according to reports from the World Health Organization [1]. In Mexico, there is a combined prevalence of overweight and obesity of 72.5%, which, when categorized by sex, is higher in women [2]. This disease has been associated with numerous cardiovascular risk factors, such as dyslipidemia, hypertension, diabetes and prothrombotic status, as well as increased mortality [3].

Total fat mass is a more accurate measure of the metabolic phenotype than body mass index (BMI). Body fat distribution is a strong metabolic and cardiovascular risk factor [4]. Different studies have recognized the existence of subtypes of obesity [5], in which it has been reported that not all obese patients show the same cardiometabolic risk, indicating the finding of obese individuals free of cardiometabolic risk factor called "Metabolically Healthy Obese" (MHO) [6,7]. On the other hand, "Metabolically Unhealthy Obese" (MUO), are those who, in addition to high BMI, have alterations in the lipid and glucose profile [8].

In addition, a proportion of those with normal BMI have been shown to have unhealthy metabolic profiles, a phenomenon referred to as the "Metabolically Unhealthy Normal Weight" (MUNW) phenotype. This group has been found to be at increased risk of diabetes, coronary heart disease, and mortality compared to those who are "Metabolically Healthy Normal Weight" (MHNW) [9].

Individuals with obesity and overweight without metabolic alterations have a higher risk of coronary heart disease and cerebrovascular

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https://doi.org/10.1016/j.thromres.2019.06.013
Received 13 March 2019; Received in revised form 19 May 2019; Accepted 20 June 2019
Available online 21 June 2019

disease compared to normal weight individuals without metabolic alterations [10]. In obesity, there is a proinflammatory state that favors acute coronary events, as well as a procoagulant state that can be evidenced through the measurement of plasminogen activator inhibitor type 1 (PAI-1); high levels of PAI-1 promote a prothrombotic environment [3].

There are differences in the inflammatory profile according to the body size phenotype, postmenopausal women displaying the MHNW phenotype present a more favorable inflammation profile than metabolically unhealthy subjects, but there is little information on the relationship of body size phenotypes with thrombosis risk [11].

The aim of this study was to determine the association between body size phenotypes and fibrinolytic activity by measuring the concentration of PAI-1 in women older than 40 years.

2. Material and methods

A cross-sectional study was performed in 230 women aged 40 to 65 years, who voluntarily attended the Endocrine Research Unit of the *Hospital de Especialidades, del Centro Médico Nacional, IMSS*. The exclusion criteria included women with an established diagnosis of diabetes mellitus, renal or liver failure, chronic infections, endocrine or blood disorders, history of cardiovascular disease or thrombosis. Subjects on treatment with statins or drugs that will affect PAI-1 expression were also excluded. The Ethics Committee of the Mexican Social Security Institute approved the study. Subjects who agreed to participate signed an informed consent form.

2.1. Clinical evaluation

Participants underwent a clinical examination; body weight, height, and blood pressure were measured. Body mass index (BMI) was calculated by dividing the weight by the square of the height (Kg/m^2). The individuals were classified as normal weight with BMI of 18 to 25, overweight with BMI of 25.1 to 29.9, and obese with a BMI of ≥30. The waist circumference was measured with the participant standing, at the midpoint of the distance between the iliac crest and the inferior border of the last rib, at the end of expiration.

Body composition was assessed by electrical bioimpedance (Body Composition 353ioi JAWON) after 12-h fasting with adequate water hydration. Bioelectric impedance was measured with the patient upright, wearing light clothing, and without shoes. The analyzer measured weight to an accuracy of within 0.1 kg, as well as body impedance (in ohms), with calculation of the visceral adipose tissue and the percentage of total body fat.

2.2. Metabolic evaluation

For this study, normal weight was considered with BMI 18.4 to 25 and the participants who were overweight and obese were grouped. To define metabolic health, the Karelis criteria were used, which were adapted for the present study. In the case of the Karelis criteria [12]: Total cholesterol ≤ 200 mg/dL, Triglycerides ≤ 150 mg/dL, High-density lipoprotein cholesterol (HDL−C) ≥ 50 mg/dL and no treatment, Low-density lipoprotein cholesterol (LDL-C) ≤ 100 mg/dL and no treatment, and HOMA-IR ≤ 2.8; with ≥4 criteria, comprised a diagnosis of metabolic healthy. Thus, participants were classified into 4 groups according to body size and metabolic health: Metabolically Healthy Normal Weight (MHNW), Metabolically Unhealthy Normal Weight (MUNW), Metabolically Healthy Obese (MHO) and Metabolically Unhealthy Obese (MUO).

Menopause diagnosis was confirmed by a serum estradiol concentration of < 25 pg/mL and amenorrhea for at least one year. None of the patients were receiving hormonal replacement therapy.

2.3. Biochemical analysis

Venous blood samples were drawn from the antecubital veins at 8:00 AM to avoid variations due to circadian rhythm and after a fast equal to or > 12 h. The samples were collected in two tubes, one containing sodium citrate and the other without anticoagulant. Samples were centrifuged at 3000 rpm for 15 min at 4 °C, and aliquots of plasma and serum were prepared for testing. Aliquots for measuring PAI-1 and insulin levels were stored at −70 °C until assayed. Glucose, total cholesterol, HDL−C, and triglycerides levels were determined in serum through the semiautomatic chemical analyzer Ekem KontroLab. LDL-C serum concentration was calculated with Friedewald's formula. High sensitivity C-reactive protein was measured by chemiluminescent immunoassay (Diagnostic Products Corporation, CA, USA). Insulin was measured by a solid-phase radioimmunoassay (Millipore, Billerica; MS, USA); the intra- and interassay coefficients of variation (CV) were 4.0% and 8.6%, respectively. Insulin resistance was evaluated through homeostasis model assessment (HOMA): HOMA-IR = insulin (mU/mL) x fasting glucose (mmol/L)/22.5 [13]. PAI-1 antigen plasma levels were measured by enzyme linked immunosorbent assay (BioVendor, NC, USA), the intra- and interassay CV were 6.0% and 5.6%, respectively.

2.4. Statistical analysis

Variables with normal distribution are expressed as mean ± standard deviation and variables with nonnormal distribution are expressed as median (interquartile range). Differences between groups were evaluated by one-way ANOVA or Kruskal-Wallis test, as appropriate. The correlation among variables was identified by Pearson's or Spearman's tests. A multivariate regression analysis was performed to determine the influence of anthropometric and metabolic variables on PAI-1 level. All analyses were performed with the statistical package SPSS v.21. A statistically significant p value was considered as $p < 0.05$.

3. Results

Two hundred seventy-seven participants were screened for eligibility, 230 women were included in the study, with a mean age of 52.3 ± 5.9 years. Of this group, 65.2% were postmenopausal women, and 27.5% had hypertension. The characteristics of the group are summarized in Table 1.

Table 1
Characteristics of participants.

Variable	
Age (years)	52.3 ± 5.9
Body weight (Kg)	68.7 ± 12.3
Body mass index (Kg/m^2)	28.8 ± 4.9
Current smoking (%)	8.8
Waist circumference (cm)	92.2 ± 11.9
Visceral adipose tissue (cm^2)	138.8 ± 57.7
Total body fat (%)	38 ± 4.5
Systolic blood pressure (mmHg)	110 (100, 120)
Diastolic blood pressure (mmHg)	70 (70, 80)
Glucose (mg/mL)	84 (76, 94)
HbA1C (%)	5.5 ± 0.6
Insulin (mU/L)	17.1 (13.0, 24.0)
HOMA-IR	3.5 (2.5, 5.3)
Triglycerides (mg/dL)	136 (110, 202)
Total-cholesterol (mg/dL)	232.6 ± 48.2
HDL-C (mg/dL)	54.9 ± 14.9
LDL-C (mg/dL)	145.6 ± 42.5
C-reactive protein (mg/L)	4.1 ± 3.5

Variables are represented as mean ± standard deviation or median (interquartile range). HOMA-IR homeostasis model assessment of insulin resistance.

Table 2
Characteristics of participants according BMI categories and metabolic health.

	Metabolically healthy normal weight	Metabolically unhealthy normal weight	Metabolically healthy obese[a]	Metabolically unhealthy obese[a]	*p*-Value
Age (years)	54.3 ± 7.8	53.1 ± 6.2	51.2 ± 6.5	52.1 ± 5.5	NS
Menopausal women (%)	60.0	67.3	61.5	65.1	NS
Weight (Kg)	58.5 ± 4.9*	56.5 ± 4.9*,§	68.2 ± 10.7	72.6 ± 11.6	0.0001
BMI (Kg/m^2)	23.1 ± 1.1*,§	23.2 ± 1.33*,§	29.2 ± 3.8	30.6 ± 4.5	0.0001
Current smoking (%)	11.1	9.4	14.2	8.9	NS
Waist circumference (cm)	79.2 ± 9.6*,§,†	81.9 ± 6.1*,§	89.6 ± 7.5*	95.7 ± 11.4	0.0001
Systolic blood pressure (mmHg)	110 (90,120)	110 (100,120)	110 (110,110)	110 (110, 120)	NS
Diastolic blood pressure (mmHg)	70 (70,80)	70 (70,80)	70 (70,70)	80 (70,80)	NS
Visceral adipose tissue (cm^2)	78.1 ± 21.1*,§	84.9 ± 24.9*,§	129.5 ± 51.1	156.0 ± 55.5	0.0001
Total body fat (%)	32 ± 2.4*,§	32.9 ± 2.8*,§	38.4 ± 3.9	39.6 ± 3.6	0.0001
Glucose (mg/dL)	73 (64,80)*,§,†	83 (76,91)	74 (74,80)*	88 (79,98)*	0.0001
HbA1c (%)	5.3 ± 0.9	5.3 ± 0.4 *	5.4 ± 0.5	5.6 ± 0.5	0.02
Insulin (mU/L)	12.2 (10.5,13.4)*	16.1 (12.4, 20.9)*	22.5 (14.3, 22.5)*	22.3 (17.1, 30.7)	0.0001
HOMA-IR	2.3 (1.7,2.7)*,§,†	3.2 (2.4, 4.7)*	4.2 (2.6, 4.9)	5.0 (3.6, 7.1)	0.0001
Triglycerides (mg/dL)	113 (80,126)*,§	137 (105, 191)	121 (83, 141)*	157 (119, 213)	0.0001
Total cholesterol (mg/dL)	180.5 ± 21.9*,†	241.5 ± 48.9§	173.2 ± 22.2*	237.4 ± 45.9	0.0001
HDL–C (mg/dL)	70.5 ± 5.2*,†	58.1 ± 15.4*,§	61.8 ± 10.2*	53.0 ± 14.8	0.001
LDL–C (mg/dL)	88.5 ± 21.6*,†	154.2 ± 45.1§	90.7 ± 20.7*	149.5 ± 39.1	0.0001
C-reactive protein (mg/L)	1.6 ± 1.4	1.9 ± 1.7*	1.9 ± 1.5*	5.4 ± 4.3	0.0001

Data are mean ± standard deviation or median (interquartile range); BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance. Differences between groups were analyzed by one-way ANOVA or Kruskal-Wallis test.

[a] Overweight participants are also included.

* $p < 0.05$ vs MUO.

§ $p < 0.05$ vs MHO.

† $p < 0.05$ vs MUNW.

Our data noted that 33.9% of participants presented MUO, 3.0% MHO, 55.3% MUNW and 7.8% MHNW, according to Karelis criteria [12]. Table 2 shows the anthropometric characteristics by phenotype. Age was similar among the 4 groups. No differences were found in body weight and BMI between MUNW and MHNW subjects, nor between groups MHO and MUO. As expected, glucose level, HOMA-IR, total cholesterol, LDL-C were reduced in MHNW compared with MUNW. MUO participants exhibited significantly increased glucose level, HOMA-IR, total cholesterol, triglycerides and LDL-C together with reduced HDL−C. On the other hand, groups MHNW and MUNW had reduced waist circumference, visceral adipose tissue, HOMA-IR and C-reactive protein in comparison with the MUO group.

The concentrations of PAI-1 in participants with normal weight was lower compared to obesity group [9.5 (0.8, 31.6) vs 18.6 (1.0, 46.1) ng/mL, respectively, $p = 0.005$]. There were no significant differences in PAI-1 level between premenopausal and postmenopausal women [13.7 (3.6, 37.5) vs 13.1(0.8, 33.9) ng/mL, NS].

PAI-1 level showed a positive correlation with BMI ($r = 0.135$, $p = 0.041$), visceral adipose tissue ($r = 0.117$, $p = 0.042$), in addition to having an association with HbA1c, glucose, triglycerides, HOMA-IR, body weight, waist circumference, insulin, total fat body mass and HDL−C, (Table 3).

The concentration of PAI-1 showed a progressive increase in MHNW, MUNW, MHO, MUO [2.3 (0.08, 13.6), 12.7, (0.08, 33.1), 23.4 (2.6, 28.8) and 22.8 (2.0, 46.7) ng/mL, respectively, $p = 0.006$] (Fig. 1).

Multiple stepwise regression of variables correlated with PAI-1 level showed that BMI and HOMA-IR influenced the concentration of PAI-1 (Table 4).

Table 3
Correlations between PAI-1 and metabolic variables.

Variable	r	*p-value*
Age (years)	0.016	0.409
Weight (Kg)	0.113	0.048
Body mass index (Kg/m^2)	0.135	0.041
Waist circumference (cm)	0.102	0.040
Systolic blood pressure (mmHg)	−0.016	0.408
Diastolic blood Pressure (mmHg)	−0.034	0.307
Visceral adipose tissue (cm^2)	0.117	0.042
Total body fat (%)	0.111	0.050
Glucose (mg/dL)	0.250	< 0.001
HbA1c (%)	0.133	0.025
Insulin (mU/L)	0.315	< 0.001
HOMA-IR	0.328	< 0.001
Triglycerides (mg/dL)	0.179	0.004
Total cholesterol (mg/dL)	0.024	0.363
HDL–C (mg/dL)	−0.200	0.002
LDL–C (mg/dL)	0.029	0.336
C-reactive protein (mg/L)	0.56	0.046

HOMA-IR, homeostasis model assessment of insulin resistance.

4. Discussion

The present study showed that concentrations of PAI-1 were increased in groups MUNW, MHO and MUO. Elevated PAI-1 promotes a state of hypofibrinolysis, which conditions a greater risk of thrombosis. As expected, patients with obesity presented elevated PAI-1; however, in this work we also found that subjects with metabolic alterations, both obese and lean, showed increased PAI-1.

Some clinical studies have confirmed increased levels of PAI-1 in patients with established atherosclerotic disease and subclinical stage of atherosclerosis [14]. Moreover, the elevated PAI-1 level produces an increase in fibrin deposits in atherosclerotic plaque [15–17].

The population with metabolic alterations in our study was high, 55.3% of patients with MUNW and 33.9% with MUO. Nevertheless, information on Mexican population is scarce. In a Peruvian study, similar frequencies were observed [18]. European studies have observed a frequency around 17–43% in MUO group [19,20], difference which may be explained by the high prevalence of obesity and metabolic disorders in Mexico [2].

There are no globally accepted criteria for the definition of metabolic phenotype; therefore, the frequency varies according to the criteria used for its classification. In the case of MHO subjects, the frequency in the present study was 3.0%, while in other studies it has been reported to be between 3 and 75% [8,15,21–24].

One observation of this study was the increase in PAI-1 in subjects in

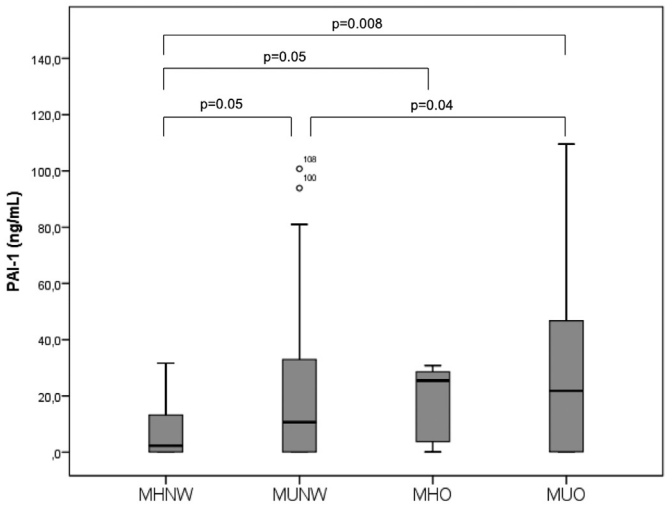

Fig. 1. PAI-1 level of Metabolically Healthy Normal Weight (MHNW), Metabolically Unhealthy Normal Weight (MUNW), Metabolically Healthy Obese (MHO) and Metabolically Unhealthy Obese (MUO). Differences between groups were analyzed Kruskal-Wallis test.

Table 4
Multiple stepwise regression analysis of variables independently associated with PAI-1 levels.

Independent variables	Standardized β	t	*p*-Value
Body Mass Index	0.149	0:358	0.05
HDL-C	−0.240	−1.744	0.06
HOMA-IR	0.266	2.867	0.005

The analysis included BMI, HDL-C and HOMA-IR. Parameters of the model: $F = 25.6$, $P < 0.001$.

the MUNW group compared with the MHNW. In spite of the fact that people with normal weight are not considered at risk, a previous study also found that this group of individuals with MUNW has a high risk of coronary disease, diabetes and higher mortality than individuals with MHNW [9]. Due to the above, lean individuals with altered metabolic phenotype also require diagnosis and follow-up.

Recently, the findings from the Nurses' Health Study showed that MUNW and MHO had increased cardiovascular disease risk compared with MHNW, which means, that metabolic status affects the prognosis of cardiovascular disease [25].

The present study used the criteria established by Karelis et al., which include metabolic variables such as cholesterol, triglycerides, HDL−C, LDL-C and HOMA-IR [12]. Hypertension is not included in these criteria. Although the mechanism is not clearly understood, hypertension leads to endothelial damage and increased PAI-1 [26–28]. However, in the present study, no differences were found in blood pressure between the groups.

Another observation in this study was the determinant effect of HOMA-IR on PAI-1 concentration. Insulin resistance has been associated with endothelial dysfunction and abnormal fibrinolysis. Thus, insulin resistance may be one mechanism through which the hemostatic factors are associated with cardiovascular disease [18]. In addition, another observation from the present study was the association between PAI-1 concentration and high triglycerides and the glucose concentrations, which all condition the progression of atherosclerosis [29].

Therefore, it is very important to employ strategies to improve metabolic health both in obese subjects as well as in lean ones with metabolic alterations [30]. Health services have recommended that doctors, especially those in first contact, focus on the population with overweight and obesity to detect abnormalities in glucose and lipids as part of their evaluation of cardiovascular risk [31]. However, from the results of this study, it might be suggested that strategies also be developed to identify metabolic alterations in patients with normal weight that may also be related with fibrinolysis reduction.

As far as we know, this is the first study focused on alteration of fibrinolysis by metabolic healthy and unhealthy phenotypes. Another strength of this study is that it was conducted in women aged 40 to 65 years. During this stage of women's life cycle, some risk factors, such as insulin resistance and abdominal fat increase, together with other changes, such as those occurring in lipid profile, increase cardiovascular risk.

One limitation of the study is its cross-sectional design. Despite this finding, we were able to identify an association between fibrinolytic activity and the metabolically unhealthy phenotype. Follow-up studies are recommended to evaluate the development of thrombotic events, especially in patients with MUNW and MUO.

Lastly, evaluation of fibrinolysis should ideally involve testing for PAI-1 antigen and activity, t-PA or plasminogen-antiplasmin (PAP) complex. Nevertheless, PAI-1 remains as the major endogenous inhibitor of fibrinolysis [32]. PAI-1 expression is positively correlated with BMI in obesity, contributing to the augmented atherothrombotic risk [33]. Consequently, we believe measurement of PAI-1 alone provides significant information of the body size phenotypes in our population. Follow-up studies with other fibrinolytic markers are recommended to evaluate thrombotic risk.

5. Conclusion

This study is the first one that recognizes differences in the fibrinolytic activity between body size phenotypes. The metabolically unhealthy phenotype, independently of BMI, showed an increase in PAI-1 level. This elevation of PAI-1 could be related to a prothrombotic state.

Acknowledgments

This study was accomplished with funding Fondo de Investigación en Salud, Instituto Mexicano del Seguro Social (FIS/IMSS/PROT/G16/1586).

Declarations of interest

None.

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