Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

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To cite this article: Lourdes Basurto, Alma Díaz, Ana Rodriguez, Ariadna Robledo, Sara Vega, Jessica Garcia-Vega & Carlos Martínez-Murillo (2019): Circulating levels of plasminogen activator inhibitor-1 are associated with metabolic syndrome rather than with menopause, Gynecological Endocrinology, DOI: 10.1080/09513590.2019.1604658

To link to this article: https://doi.org/10.1080/09513590.2019.1604658

Published online: 26 Apr 2019.

GYNECOLOGICAL ENDOCRINOLOGY
https://doi.org/10.1080/09513590.2019.1604658

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ORIGINAL ARTICLE

Circulating levels of plasminogen activator inhibitor-1 are associated with metabolic syndrome rather than with menopause

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ABSTRACT

The plasminogen activator inhibitor type 1 (PAI-1) is the major determinant of fibrinolytic activity. PAI-1 concentrations are elevated in obesity, type 2 diabetes and metabolic syndrome (MetS). On the other hand, during menopause, fibrinolytic activity decreases and, consequently, PAI-1 concentration increases; however, it is debated whether menopause is an independent determinant factor of PAI-1 levels. The objective of this study was to evaluate the effect of hormonal and metabolic status on the concentration of PAI-1 in pre-and post-menopausal women. A case-control study was conducted in ninety pre-and post-menopausal women aged 45 to 55 years, matched by body mass index (BMI). Anthropometric measurements and biochemical determinations were performed on all participants. The fibrinolytic activity was determined by measuring PAI-1 by ELISA. Of all the women, 30% presented MetS. Women with MetS had higher values of PAI-1 (36.0 ± 19.1 vs 19.3 ± 14.8 ng/mL, $p < .001$); in contrast, no differences were observed when compared by hormonal status (20.7 ± 18.10 vs 20.2 ± 17.0 ng/mL, NS). The results of this study suggest that in women, MetS plays a more important role in the deterioration of the fibrinolytic mechanisms rather than their hormonal status. Therefore, the identification of cardio-metabolic factors is relevant to reduce the presence of thrombosis in post-menopausal women.

ARTICLE HISTORY
Received 30 September 2018
Accepted 4 April 2019
Published online 24 April 2019

KEYWORDS
PAI-1; menopause; atherosclerosis; fibrinolysis; metabolic syndrome

Introduction

Myocardial infarction, stroke, and venous thromboembolism represent the most frequent causes of cardiovascular death. Post-menopausal women have a higher risk of ischemic heart disease than pre-menopausal women, which shows that estrogen deficiency contributes to an increased risk of cardiovascular disease [1]. It has been reported that post-menopausal women have elevated levels of plasminogen activator inhibitor type-1 (PAI-1), suggesting deterioration of the fibrinolytic system, which is considered an independent factor for atherosclerosis [2,3]. Several studies have reported a strong, independent relation between low fibrinolytic activity and ischemic heart disease [3].

PAI-1, a regulatory protein in the coagulation system, is the primary inhibitor of fibrinolysis, by inactivating tissue-type plasminogen activator [4]. PAI-1 is synthesized mainly in the vascular endothelium, liver, platelets, vascular smooth muscle and adipose tissue [5]. High PAI-1 concentrations have been positively associated with risk factors that contribute to atherosclerosis. Imbalance in the fibrinolytic state caused by increased plasma levels of PAI-1, may contribute to the progression of the atherosclerosis process by stabilizing the fibrin layer and depositing extracellular matrix at the site of endothelial injury. The expression of PAI-1 in atherosclerotic lesions strongly suggests it plays an important role in atherogenesis [5].

There are other factors that affect PAI-1 concentrations, such as age and obesity. Several clinical studies have shown increased PAI-1 concentrations in patients with obesity, diabetes mellitus and metabolic syndrome (MetS) [6]. Insulin resistance has been associated with endothelial dysfunction and abnormal fibrinolysis. The mechanisms by which insulin resistance influences hemostatic factors are complex. However, it has been observed that high levels of insulin increase the synthesis of PAI-1 [7].

Post-menopausal women have an increased cardiovascular risk due to changes in their body fat distribution, lipid profile, insulin resistance and hypofibrinolysis [7,8]. However, the relationship between PAI-1 levels and menopause is still controversial. Therefore, the objective of the present study was to assess the effects of metabolic status on PAI-1 concentrations in pre- and post-menopausal women.

Material and methods

A case-control study was carried out in 90 pre- and post-menopausal women, who were matched by BMI and were found to be healthy, within an age range of 45–55 years, in the Endocrine Diseases Medical Research Unit, Hospital de Especialidades del Centro Médico Nacional Siglo XXI, IMSS. The exclusion criteria were: personal history or clinical data of cardiovascular or cerebrovascular disease, diabetes, liver and kidney failure, chronic infection, endocrinopathy, hematological disease and subjects on treatment with lipid-lowering agents. Participants who were found to be under hormone treatment were also excluded. The present study was approved by the Research Committee of the 'Instituto Mexicano del Seguro Social'. The volunteers were

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informed of the research and its aim and requested to sign consent after accepting to participate.

All women underwent a clinical examination and anthropometric measures were taken. Weight and height were determined with a stadiometer with a precision of 1 mm. The BMI was calculated, and the waist circumference was measured. The diagnosis of post-menopause was established by amenorrhea ≥1 year, FSH level ≥30 mU/mL and estradiol ≤30 pg/mL.

MetS was defined based on the International Diabetes Federation Consensus criteria when women presented 3 or more of the following criteria: abdominal circumference ≥80 cm, hypertriglyceridemia ≥150 mg/dL, high-density lipoprotein cholesterol (cHDL) ≤50 mg/dL, systolic hypertension ≥130 mmHg or diastolic ≥90 mmHg or use of antihypertensive pharmacological therapy and high fasting glucose ≥100 mg/dL [9,10].

Body analysis was performed by bioelectrical impedance with the JAWON 353 IOI Body Composition Analyzer. The analysis was performed after a 12-h fast, with adequate hydration. The value of visceral adipose tissue (VAT) was obtained.

Biochemical analysis

Venous blood samples were taken between 8:00 and 8:30, after a 10-h fast. The blood sample was obtained in two tubes, one containing sodium citrate and the other without anticoagulant. The samples with citrate and without anticoagulant were centrifuged at 3000 rpm for 15 min at 4 °C. The aliquots for the measurement of hormones were stored at −70 °C until the test was performed. Glucose, high-density lipoprotein cholesterol (cHDL) and triglycerides were detected by enzymatic methods, using the chemistry analyzer Ekem KontroLab. Low-density lipoprotein cholesterol (cLDL) levels were calculated with the Friedewald formula.

Serum insulin and estradiol levels were measured by radioimmunoassay. Insulin was measured using reagents from Millipore Co. (Bellerica, MA, USA); sensitivity was 2.7 μU/mL and intra- and inter-assay coefficients of variation (CVs) were 5.2 and 7.3%, respectively. Estradiol was measured using reagents from Diagnostic Products Co. (Los Angeles, CA, USA); sensitivity was 10 pg/mL and CVs were 4.0 and 8.6%. The insulin resistance index was evaluated by HOMA (homeostasis model assessment) according to Matthews formula: fasting insulin (μU/mL) X fasting glucose (mg/dL)/405 [11]. Plasma concentrations of PAI-1 were measured by enzyme-linked immunosorbent assay (Bio Vendor LLC, Candler NC, USA); sensitivity was 0.2 ng/mL, the intra- and inter-assay CVs were 6.0 and 5.6%, respectively.

Statistical analysis

By the type of distribution of the variables, nonparametric tests were used. To identify the correlation between the variables, the Spearman test was performed. To detect the differences between the groups, the Mann–Whitney *U* test was used. Kruskal–Wallis test was applied to identify differences between PAI-1 levels according to number of MetS components, *post hoc* comparisons were performed with Mann–Whitney test with a Bonferroni correction. Statistical power calculations were performed to detect a difference in PAI-1 levels of 30%, which revealed the need for 41 participants per group to achieve a power of 0.90 [12]. Statistical level of significance was defined by two-tailed test with $p < .05$. All the analysis was carried out with the statistical program SPSS v.20.

Results

From which 90 patients, 45 women were in post-menopausal stage and 45 women in pre-menopausal stage. 30% of the total participants presented MetS. Post-menopausal women showed increased age, total cholesterol, cLDL, and VAT; along with significantly lower estradiol levels in comparison with pre-menopausal women. The concentration of PAI-1 did not present a significant difference between pre and post-menopausal women (Table 1).

When performing the metabolic analysis, glucose, triglycerides, HbA1c, HOMA-IR, VAT, and estradiol concentrations were higher in women with MetS (Table 2). However, the concentrations of PAI-1 were higher in women with MetS compared to participants without it (36.0 ± 19.1 vs 19.3 ± 14.8 ng/mL, $p < .001$).

PAI-1 levels were correlated with BMI ($r = 0.0221$, $p < .05$), glucose ($r = 0.276$, $p < .01$), triglycerides ($r = 0.262$, $p < .01$), cHDL ($r = -0.305$, $p > .01$), HOMA-IR ($r = 0.307$, $p < .001$), VAT (0.162, $p < .05$). An association between the presence of components for MetS and PAI-1 levels can be observed,

Table 1. Biochemical and anthropometric characteristics of the participants according to hormonal status.

	Hormonal status		
	Pre-menopause($N = 45$)	Post-menopause($N = 45$)	*p* value*
Age (years)	46.4 ± 2.4	54.8 ± 4.3	.0001
Weight (Kg)	70.4 ± 14.1	69. 2 ± 12.8	NS
BMI (Kg/m^2)	29.2 ± 5.3	29.1 ± 5.3	NS
Waist circumference (cm)	91.3 ± 12.5	90.6 ± 17.9	NS
Systolic pressure (mmHg)	107.9 ± 13.1	111.2 ± 11.7	NS
Diastolic pressure (mmHg)	72.3 ± 8.4	75.3 ± 7.5	.051
VAT (cm^2)	125.02 ± 52.2	142.03 ± 60.4	.03
Glucose (mg/dL)	81.6 ± 14.7	84.0 ± 13.8	NS
Total cholesterol(mg/dL)	209.3 ± 33.7	235.7 ± 52.7	.02
Triglycerides (mg/dL)	153.7 ± 82.9	155.4 ± 62.6	NS
cHDL (mg/dL)	53.6 ± 12.7	53.4 ± 13.3	NS
cLDL (mg/dL)	124.9 ± 36.5	149.8 ± 45.3	.03
HbA1c (%)	5.4 ± 0.4	5.5 ± 0.4	NS
HOMA-IR	3.8 ± 2.6	4.1 ± 2.3	NS
Estradiol (pg/mL)	94.7 ± 45.8	34.1 ± 26.7	.04
PAI-1(ng/mL)	20.7 ± 18.10	20.2 ± 17	NS

The data is shown with the mean ± standard deviation.
HOMA: the homeostasis model assessment; VAT: visceral adipose tissue; PAI-1: Plasminogen activator inhibitor-1, NS: Not significant.
*To identify the differences between the groups, the Mann–Whitney *U* test was used.

Table 2. Biochemical and anthropometric characteristics of the participants according to metabolic syndrome (MetS).

	Metabolic profile		
	MetS ($n = 27$)	Without MetS ($N = 63$)	p value*
Premenopause/Postmenopause	12/15	33/30	NS
Age (years)	51.8 ± 6.0	50.0 ± 5.1	NS
Weight(Kg)	75.7 ± 14.9	67.3 ± 11.9	.002
BMI (Kg/m^2)	32.1 ± 5.8	27.9 ± 4.5	NS
Waist circumference (cm)	94.9 ± 22.1	89.2 ± 11.0	NS
Systolic pressure (mmHg)	115.2 ± 14.2	107.1 ± 10.8	.001
Diastolic pressure (mmHg)	76.7 ± 9.1	72.6 ± 5.1	.004
Glucose(mg/dL)	91.5 ± 16.4	79.1 ± 11.4	.001
Cholesterol(mg/dL)	223.6 ± 53.1	221.9 ± 42.9	NS
Triglycerides (mg/dL)	203.7 ± 84	133.4 ± 56.5	.0001
cHDL (mg/dL)	42.1 ± 10.3	58.4 ± 10.8	.0001
cLDL(mg/dL)	138.1 ± 48.3	136.8 ± 40.6	NS
HbA1c (%)	5.7 ± 0.5	5.4 ± 0.3	.04
HOMA-IR	5.3 ± 2.9	3.4 ± 2.0	.002
Estradiol(pg/mL)	31.8 ± 33.3	14.3 ± 18.7	.05
VAT (cm^2)	163.9 ± 60.8	122.7 ± 50.6	.001
PAI-1 (ng/mL)	36.0 ± 19.1	19.3 ± 14.8	.002

The data is shown with the mean ± standard deviation.
HOMA-IR: the homeostasis model assessment; VAT: visceral adipose tissue; PAI-1: Plasminogen activator inhibitor-1, NS: Not significant.
*To identify the differences between the groups, the Mann–Whitney *U* test was used.

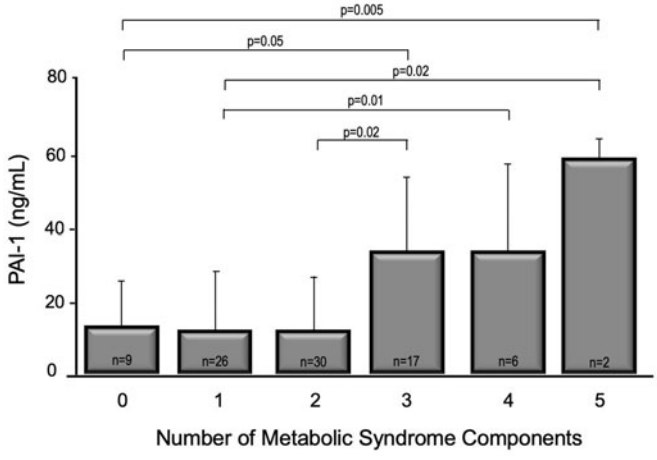

Figure 1. PAI-1 levels according to the number of Metabolic Syndrome (MetS) components, independent of hormonal status. Participants with three components had higher PAI-1 levels compared with women without MetS. The differences between the groups were calculated using the Kruskal–Wallis test, *post hoc* comparisons were performed with Mann–Whitney test and Bonferroni correction. Data are presented as mean ± standard deviation.

as the participants without MetS had lower levels of PAI-1 than women with MetS (Figure 1).

Discussion

In this study, it was observed higher PAI-1 levels related to MetS and not menopausal status, once women were matched by BMI [13].

Although estrogens influence the expression of PAI-1, they also contribute to the distribution of adipose tissue. Estrogens have different effects on the adipose tissue; these hormones regulate the growth and location of adipocytes, reduce and modulate the production and release of adipokines, and it has been proposed that estrogens affect adipose tissue through modulation of lipolytic activity [14,15]. However, in the present study, there were no differences in PAI-1 concentrations when comparing pre-and post-menopausal women, since the BMI was controlled by matching the participants.

Adipose tissue is an important source of PAI-1, which contributes directly to the plasma increase of this adipokine in obesity [16]. VAT has been considered the main contributor to the increase of PAI-1 levels in obese subjects [17,18]. In a study conducted by Cigolini M. et al, which included 52 men with different degrees of BMI and body fat distribution, it was found that PAI-1 activity was higher in obese men with greater area of VAT [19]. Therefore, VAT can be a source of active adipokines and PAI-1. In the present study, the association between PAI-1 levels and VAT is shown.

On the other hand, MetS is characterized as being a low-grade chronic inflammatory state where various inflammatory cytokines are produced, such as TNF-α; which increases the expression of PAI-1 in adipose tissue [18]. Overexpression of PAI-1 in obesity is a complex process and it is most likely that several factors contribute to this phenomenon, such as MetS, inflammation, oxidative stress, insulin resistance, hypoxia, and the renin-angiotensin axis [18]. Additionally, PAI-1 concentrations have been associated with the different components of MetS, especially with glucose levels, lipid profile, insulin resistance and increased adipose tissue [20–23].

On the other hand, in this study, it was observed that women with MetS had a higher estradiol level, although in both MetS and without MetS groups there was no difference in proportion of pre- and post-menopausal women. Women with MetS had a higher BMI. Obesity can influence the rate of estradiol decline during menopause. Sowers et al. reported the mean rates of estradiol decline in obese women were half those observed in non-obese women. Slower rates of estradiol loss during menopause resulted in higher circulating estradiol levels among obese women [24].

In the present study, PAI-1 levels were directly proportional to the number of components in the MetS. In a previous study, an association was observed between PAI-1 and the number of components that define MetS, which was stronger than the correlation between the factors themselves [25], consequently, suggesting that MetS may play an important role on the variability of PAI-1 levels.

The results of the present study suggest that although estrogen influences PAI-1 concentrations, MetS seems to have a greater influence. To our knowledge, this is the first study that compares the effects of menopause and metabolic status on PAI-

1 concentrations, suggesting that the presence of elevated levels of PAI-1 in post-menopausal women with MetS could be of great relevance in the determination of cardiovascular risk in this target population.

In the present study, a relatively small number of women were included in the analysis; however, BMI matching led to unbiased results even with a relatively small sample. The main strength was the study design, a case-control matched for BMI.

Conclusion

The results of this study suggest that in women, MetS seems to play a more important role in the deterioration of the fibrinolytic mechanisms rather their hormonal status. Therefore, the identification of metabolic factors is relevant to reduce the presence of thrombosis in post-menopausal women.

Acknowledgments

The authors thank Susan Drier-Jones for her assistance with the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported in part by a scientific grant from Consejo Nacional de Ciencia y Tecnología (2013–01-201874).

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