Association of hormonal state with cardiovascular risk evaluated with Globorisk in Mexican women

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Abstract

Introduction: Cardiovascular disease is the main cause of mortality worldwide. In women, its incidence increases at the sixth decade of life, coinciding with postmenopause. Whether this effect is due to menopause-related hormonal changes is not known.

Objective: To evaluate the differences in cardiovascular risk in pre- and postmenopausal women by means of the Globorisk risk scale, the triglyceride/high-density lipoproteins cholesterol (Tg/HDL-C) ratio and metabolic syndrome (MS) criteria. **Method:** Cross-sectional study that included 408 women from 40 to 60 years of age; anthropometric measurements and biochemical determinations were performed. The participants were classified as premenopausal and postmenopausal. Cardiovascular risk was assessed using the MS criteria, the Globorisk risk calculator and the Tg/HDL-C ratio. **Results:** Postmenopausal women showed a significant increase in waist circumference, total cholesterol and triglycerides in comparison with premenopausal women. Significant associations were found between hormonal state and Globorisk measured cardiovascular risk (OR = 2.50; 95 % CI = 1.67-3.74) and the Tg/HDL-C ratio (OR = 1.66; 95 % CI = 1.09-2.52). **Conclusion:** Cardiovascular risk factors have a higher prevalence in postmenopause. The Globorisk scale and Tg/HDL-C ratio identify cardiovascular risk in postmenopausal women.

KEY WORDS: Menopause. Cardiovascular disease. Globorisk. Metabolic syndrome. Triglyceride/HDL-cholesterol ratio.

Introduction

The main cause of mortality in the world both in men and women is cardiovascular disease (CVD),¹ which represents a serious problem for many Latin American countries;² in Mexico, one woman dies every 15 minutes due to CVD.³ Morbidity and mortality from this cause is more common in men than in women until the sixth decade of life;⁴ in the female population, it appears 10 to 15 years later, a stage that coincides with postmenopause.⁵ Building upon this observation, multiple studies have been carried out to identify whether hypoestrogenism during menopause directly or indirectly increases CVD when the prevalence of risk factors such as dyslipidemia, diabetes mellitus (DM), overweight and arterial hypertension (AH) is increased.⁶

There are more than 100 cardiovascular risk prediction models, including the metabolic syndrome (MS) criteria,⁷ the triglyceride/HDL-C index (Tg/HDL-C)⁸ and the Framingham scale;⁹ however, many of them have not been validated beyond the populations where they were developed.¹⁰ In relation to this, the Globorisk risk scale was published, which is an adaptation of the Framingham tables for different countries, including Mexico. In this studio, Mexican women aged 40 to 84 years were observed to be at second place of CVD risk.^{11,12}

Multiple cross-sectional and longitudinal studies have been carried out to identify if menopause is a cardiovascular risk (CVR) factor that is independent of age or body mass index (BMI), with results not yet conclusive.¹³

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The present investigation was carried out with the purpose to identify the association between the menopausal status and some tools to assess CVR, such as Globorisk, the MS criteria and the Tg/HDL-C index, as well as to find out the differences in independent risk factors between premenopausal and postmenopausal women.

Method

Comparative, cross-sectional study in 710 women of 40 to 60 years of age and apparently healthy, who attended the Medical Research in Endocrine Diseases Unit of *Siglo XXI* National Medical Center of the Mexican Institute of Social Security in Mexico City. Women diagnosed with diabetes, liver failure, kidney disease, chronic infections, endocrinopathies, hematologic diseases or with a history of CVD were excluded. In addition, pregnant women, women with surgical menopause or who were on treatment with hormone replacement therapy were excluded. Finally, 408 women who met the selection criteria were selected.

This protocol was approved by the Mexican Institute of Social Security ethics committee. The participants were briefed on the study and signed the respective informed consent.

The participants were taken a medical history and underwent complete physical examination, where anthropometric measurements were recorded; height and weight were measured without shoes and with light clothing. Systolic and diastolic blood pressure was measured with an aneroid sphygmomanometer, in both arms, and the average of both measurements was used as final value. The participants were classified according to their BMI as having normal weight (BMI ≥ 18 to 24.9), overweight (BMI ≥ 25 to 29.9) or obesity (BMI ≥ 30). Abdominal obesity was considered when waist circumference was > 80 cm.

Antecubital venous blood samples were obtained at between 07:00 and 08:00 hours, after a fasting of more than 12 hours; the samples were collected in tubes without anticoagulant. The samples were centrifuged at 3500 rpm for 15 minutes to separate aliquots, which were kept frozen at -70°C until the performance of the tests. Glucose, high density lipoprotein cholesterol and triglyceride quantification was carried out in serum using the Ekem® semi-automated chemical analyzer (KontroLab). Low-density lipoprotein cholesterol (LDL-C) was calculated with Friedewald's LDL-C formula.¹⁴

Menopause was clinically defined by amenorrhea for more than 12 months and biochemically by follicle stimulating hormone (FSH) serum concentrations > 30 mU/mL and estradiol < 30 pg/mL. The participants who were at perimenopause with irregular menstrual cycles or from had 3 to 12 months of amenorrhea were excluded from the study.

Cardiovascular risk was estimated by means of the Globorisk risk scale,¹¹ which evaluates the following parameters: systolic blood pressure, total cholesterol, diabetes, smoking, age and gender. Based on this, five 10-year fatal cardiovascular risk categories were identified: $< 3\%$, 3-6 %, 7-9 %, 10-14 %, and $\geq 15\%$. For the purposes of this study, two groups were considered: women with $< 1\%$ risk and a second group with $\geq 1\%$ probability of having a fatal cardiovascular event at 10 years.¹⁵

MS was evaluated with the Harmonizing the Metabolic Syndrome consensus criteria, with the presence of at least 3 of the 5 following criteria:⁶

- Waist circumference > 80 cm for women.
- Triglycerides (Tg) ≥ 150 mg/dL or intake of hypertriglyceridemia treatment.
- HDL cholesterol (HDL-C) < 50 mg/dL.
- Systolic blood pressure ≥ 130 mm Hg or diastolic ≥ 85 mm Hg, as well as a history of high blood pressure with or without treatment.
- Fasting glucose ≥ 100 mg/dL.

The Tg/HDL-C index was obtained by dividing the serum triglyceride levels by HDL-C concentrations. High risk was considered when the index was ≥ 3.0 and lower risk with an index < 3.0 .¹⁶

In order to identify the distribution of variables, normality tests such as mental methods, bias, kurtosis and the Kolmogorov-Smirnov test were used. Parametric variables are represented with the mean and standard deviation (SD), whereas for nonparametric variables, medians and interquartile ranges (IQR, 25-75%) were used.

Hormonal status, MS and each of its components and the Tg/HDL-C index were considered as dichotomous qualitative variables. The number of SM components and Globorisk scale-measured cardiovascular risk were considered as ordinal variables, whereas the type of dyslipidemia was regarded as a polytomic variable. The remaining variables were considered to be quantitative.

To identify the mean differences between the premenopausal and postmenopausal women groups, Student's t-test was used for independent samples, whereas for nonparametric variables, Mann-Whitney's

U-test was used. For qualitative variables, the chi-square test was used. To identify correlations, Pearson or Spearman's correlation coefficients were used according to the variable distribution. Risk was calculated with the odds ratio (OR) and 95 % confidence intervals (CI); for adjustment by age, the beta exponent was used. A p-value < 0.05 was considered to be statistically significant. The statistical analysis was carried out with the SPSS program, version 21.

Results

Of 710 women, 408 who met the selection criteria were included; of them, 178 (43.6 %) were premenopausal women and 230 (56.4 %) were at postmenopausal stage. Differences were observed between pre- and postmenopausal women in age (46.0 ± 3.3 years versus 52.5 ± 3.9 years, $p = 0.001$), waist circumference (88.7 ± 11.8 cm versus 91.3 ± 11.6 cm, $p = 0.025$), total cholesterol (230.2 ± 45.8 mg/dL versus 241.1 ± 51.8 mg/dL, $p = 0.027$), triglycerides (121 mg/dL, IQR = 93-165 versus 138 mg/dL, 108-192 mg/dL, $p = 0.01$); and in Tg/HDL-C index (2.62 mg/dL, IQR = 1.76-3.5 versus 2.89 mg/dL, 1.88-4.47, $p = 0.039$). General characteristics of the population are shown in Table 1. In addition, a prevalence of overweight and obesity of 78.3 % was found in both groups, 77.4 % in premenopausal and 79 % in postmenopausal women (Table 2).

Postmenopausal women showed a higher prevalence of MS and Tg/HDL-C index elevation; however, the differences were not significant (Table 2). In contrast, risk distribution according to the Globorisk scale was different between pre- and postmenopausal women (Table 2). Based on the cutoff point of 3 %, which defines very low cardiovascular risk (< 3 %) or low cardiovascular risk (> 3 %), the prevalence of this risk in the group of premenopausal women was 1.2 %, and in the postmenopausal group, 2.3 %. Therefore, cardiovascular risk based on the Globorisk scale was dichotomized as <1 % or ≥ 1 %. Postmenopausal women showed a higher proportion in estimated risk for fatal cardiovascular disease (> 1 %) in comparison with premenopausal women, as shown in figure 1. Similarly, significant differences were found in the Tg/HDL-C index (Fig. 1).

The risk for hyperglycemia, hypertension and hypertriglyceridemia was observed to be higher in postmenopause (Table 3). In addition, the postmenopausal stage was associated with higher risk of cardiovascular events as assessed by the Globorisk scale, with

an OR = 2.50 (95% CI = 1.67-3.74), and with the Tg/HDL-C index, with an OR = 1.66 (95% CI = 1.09-2.52). However, when adjustment was made for age, these associations disappeared, except in the subgroup of women of 45 to 49 years of age, where the association was with the Tg/HDL-C index, with an OR = 2.35 (1.02-5.39) (Table 3).

Discussion

This study demonstrated that, during the postmenopausal stage, women show a CVR increase as assessed by the Globorisk scale and the Tg/HDL-C index. Identification of risk during the postmenopausal stage can be useful in CVD prevention. During this stage, women are known to have more visceral adipose tissue and an altered lipid profile in comparison with premenopausal women, which can contribute to a CVR increase during postmenopause.¹⁷

In contrast, no significant differences were found in this study in the prevalence of MS between pre- and postmenopausal women. MS increases the risk of mortality to a greater extent in women versus men, although controversy remains on whether menopause is an age-independent risk factor for CVD.¹⁸

This study identified a prevalence of MS of 42.9 % in postmenopausal women, similar to that reported in other countries where prevalence ranges from 26.1 to 54.6 %, including a study in Mexico where a prevalence of 31 % was reported.¹⁹ The differences in prevalence are partly explained by the criteria that are used for diagnosis. In a previous study in women, MS prevalence in postmenopause was 44.4 % with the ATP-III-NCEP criteria and 61.5% with the International Diabetes Federation criteria.²⁰

The Tg/HDL-C index has been associated with insulin resistance, and this in turn with CVD.²¹ However, there are differences regarding the cutoff point in each population to identify insulin resistance. In this work, a cutoff point of 3.0 was used, similar to a previous study in a Mexican population, where high correlation with insulin resistance was demonstrated.¹⁶ Similarly, an increase in the Tg/HDL-C index in postmenopausal women has been observed in other works, and this index has been shown to be a useful MS predictor.²²

Several investigations have been carried out with the purpose to identify whether menopause increases CVR, and for that purpose, risk calculators have been used, including SCORE.²³ A previous work identified that, with this scale, there is a significant risk increase in postmenopausal women.²³

Table 1. General characteristics of the population according to pre- and postmenopausal hormonal status

Variable	Total (n = 408)		Premenopause (n = 178)		Postmenopause (n = 230)		p
	Mean ± SD		Mean ± SD		Mean ± SD		
Age (years)	49.6 ± 4.8		46.0 ± 3.3		52.5 ± 3.9		0.001
Weight (kg)	68.7 ± 12.3		68.9 ± 13		68.5 ± 11.7		0.74
Height (m)	1.54 ± 0.05		1.55 ± 0.05		1.53 ± 0.07		0.290
Waist circumference (cm)	90.2 ± 11.7		88.7 ± 11.8		91.3 ± 11.6		0.025
BMI	28.7 ± 5.0		28.2 ± 5.3		28.8 ± 4.7		0.88
Systolic BP (mm Hg)	113.6 ± 14.3		112.1 ± 14		114.7 ± 14.6		0.069
Diastolic BP (mm Hg)	76.9 ± 9.2		76.4 ± 9.8		77.3 ± 8.8		0.339
Glucose (mg/dL)	88.5 ± 22.2		87.2 ± 20		89.5 ± 23.8		0.304
Triglycerides (mg/dL)	130 (101-189)		121 (93-165)		138 (108-192)		0.010
Total cholesterol (mg/dL)	236.4 ± 49.5		230.2 ± 45.8		241.1 ± 51.8		0.027
HDL-C (mg/dL)	51.4 ± 14.9		51.2 ± 13.7		51.5 ± 15.8		0.822
LDL-C (mg/dL)	154 ± 47.7		148.9 ± 47.5		157.9 ± 47.5		0.071
	Mediana	IQR	Mediana	IQR	Mediana	IQR	
Tg/HDL-C index	2.7	1.8-4.1	2.60	1.76-3.50	2.89	1.88-4.47	0.039
Estradiol (pg/mL)	48.2	20.7-101	77.5	49-140	19.7	9.3-40.2	0.001
MS components	%		%		%		
0	5.9		7.2		5.1		0.15
1	22.8		24.0		21.7		
2	30.6		32.5		29.3		
3	25.0		21.4		27.3		
4	11.4		11.9		12.1		
5	4.3		3.0		4.5		

IQR = 25-75 % interquartile range, BMI = body mass index, BP = blood pressure, MS = metabolic syndrome.

In the described study, a large proportion of participants were found to have low CVD risk (< 3 %) and no women were found with high or very high risk, since diabetic patients were excluded.¹¹ Conversely, in Globorisk original report, a prevalence of fatal risk was identified in 69 % of Mexican women; it should be noted that, in this work, the women's age range was from 40 to 80 years of age and population with diabetes was included.¹¹

In Globorisk second report, where cardiovascular risk was assessed based on biochemical and clinical factors and that was recalibrated for 182 countries, cardiovascular risk was observed to be increasing in developing countries in comparison with developed countries.¹² The calibrated evaluation for Mexico, with

a 15-year projection, was 11 % for women aged 40 to 84 years.¹¹

Recalibration of the scale to each country and to each population would allow for the Globorisk prediction model to be improved and this way it could serve to establish CVD prevention strategies.

The prevalence of risk factors varies according to the population, genetic profile, age, dietary habits, lifestyle, physical activity, gender and hormonal status, and thus we consider this study to be a contribution for CVR identification in the female population. To the best of our knowledge, this is the first prospective study conducted using the Globorisk cardiovascular risk scale in women aged 40 to 60 years, since in this group of patients there is an increased risk for CVD.

Table 2. Distribution of main risk factors in pre- and postmenopausal women

Variable	Total (n = 408)	Premenopause (n = 178)	Postmenopause (n = 230)	p
	%	%	%	
Abdominal obesity				
Without	16.8	20.0	14.4	0.13
With	83.2	80.0	85.2	
BMI				
Normal	21.7	22.6	21.0	0.22
Overweight	41.4	43.5	39.7	
Obesity	36.9	33.9	39.3	
Arterial hypertension				
Without	66.1	68.	64.4	0.49
With	33.9	31.4	35.6	
Smoking habit				
Without	68.4	69.1	67.8	0.78
With	31.6	30.9	32.2	
Hyperglycemia				
Without	82.8	83.1	82.6	0.99
With	17.2	16.9	17.4	
Hypertriglyceridemia				
Without	59.7	65.9	51.7	0.44
With	40.3	34.1	42.2	
Decreased HDL-C				
Without	49.3	50.3	48.6	0.82
With	50.7	49.7	51.4	
Metabolic syndrome				
Without	59.3	62.7	57.1	0.31
With	40.7	37.3	42.9	
Elevated Tg/HDL-C index				
Without	57.1	64.2	51.9	0.24
With	42.9	35.	48.1	
GloboRisk				
< 1	52.0	64.4	42.2	0.05
1	40.7	32.1	47.7	
2	5.4	2.3	7.8	
3	1.7	0.6	2.3	
4	0.2	0.6	0	

BMI = body mass index, Tg = triglycerides.

Table 3. Association of risk factors with postmenopausal status

Variable	n*	%	OR (95 % CI)	OR (95 % CI)**
Abdominal obesity risk	198/408	85.6	1.48 (0.88-2.50)	1.27 (0.63-2.54)
Hypertension risk	69/408	24.8	3.12 (1.74-5.38)	0.44 (1.43-1.73)
Hyperglycemia risk	40/408	17.4	1.03 (0.61-1.74)	1.19 (0.56-2.55)
Hypertriglyceridemia risk	103/404	44.9	1.57 (1.03-2.39)	0.92 (0.52-1.65)
HDL-C risk	120/404	51.4	1.07 (0.71-1.61)	1.52 (0.85-2.70)
Metabolic syndrome	106/404	61.1	1.26 (0.80-1.99)	0.97 (0.52-1.81)
Tg/HDL-C index	112/404	48.1	1.66 (1.09-2.52)	1.36 (0.76-2.43)
Tg/HDL-C (45-49 years)	19/118	48.7	2.33 (1.04-5.11)	2.35 (1.02-5.39)
GloboRisk	133/408	57.8	2.50 (1.67-3.74)	1.06 (0.61-1.84)

*Postmenopausal population. **Age-adjusted. OR = odds ratio, Tg = triglycerides.

Figure 1. Differences in metabolic syndrome frequency, triglyceride/HDL cholesterol index (Tg/HDL-C) increase and Globorisk scale-assessed cardiovascular risk in pre- and postmenopausal women.

One limitation of the investigation lies in that the assessment was aimed at non-diabetic population and, therefore, the results show lower cardiovascular risk than that which can be observed in the general population. However, based on the results, it should be insisted on that, during the climacterium, cardiovascular disease prevention should be continued in apparently healthy women.

In summary, the data showed that cardiovascular risk factors have a higher prevalence during postmenopause, even in non-diabetic population. The Globorisk scale and the Tg/HDL-C index allow for the

increase in cardiovascular risk to be identified in postmenopausal woman.

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