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Complete List of Authors:	Cagnacci, Angelo; Azienda Policlinico di Modena, Palma, Federica; Azienda Policlico di Modena, Romani, Cecilia; Azienda Policlico di Modena, Xholli, Anjeza; Azienda Policlico di Modena, bellafronte, manuela; Azienda Policlico di Modena, Di Carlo, Costantino; Università Federico II di Napoli,
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Are climacteric complaints associated with risk factors of cardiovascular disease in perimenopausal women?

Angelo Cagnacci MD, PhD[1], Federica Palma MD[1], Cecilia Romani MD[1], Anjeza Xholli MD[1], Manuela Bellafronte MD[1], Costantino Di Carlo MD[2].

[1]Department Obstetrics Gynecology and Pediatrics, Obstetrics and Gynecology Unit, Azienda Ospedaliero-Universitaria of Modena, Italy

[2]Department of Neuroscoiences and Reproductive Sciences, University of Naples Federico II, Naples , Italy.

Correspondence to: Angelo Cagnacci MD, PhD, Dipartimento Integrato Materno-Infantile, Ginecologia e Ostetrica, Azienda Ospedaliero-Universitaria di Modena, via del Pozzo 71, 41100 Modena, Italy.

Tel 39 059 4222851; Fax 39 059 4224394; email cagnacci@unimore.it

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Abstract

Recent studies indicate that metabolic risk for cardiovascular disease is increased in postmenopausal women suffering from disturbances such as hot flushes. In order to evaluate whether this is true also in peri-menopausal women we performed an observational study on 590 peri-menopausal women of an outpatient center at a University Hospital. Each cardiovascular risk factor such as blood pressure, fasting glucose, fasting lipids and the ten year risk for cardiovascular disease was tested for its relation to climacteric complaints. The Greene's climacteric scale, and its subscales were used to evaluate climacteric symptoms. Analyses were corrected for confounders derived by personal history and anthropometric measures. When corrected for confounders the Greene's score was a positive determinant of triglycerides (R^2=0.249; p=0.0001), triglycerides/HDL-cholesterol (R^2=0.316; p=0.0001), glucose (R^2=0.101; p=0.0003), and the 10-year risk for cardiovascular disease, calculated by the Framingham formula (R^2=0.081; p=0.0001). The Greene's vasomotor sub-score was an independent determinant of LDL-cholesterol (R^2=0.025; p=0.01), and LDL/HDL-cholesterol (R^2=0.143;p=0.0001), while the Greene's depression sub-score was a negative determinant of HDL-cholesterol (R^2=0.179; p=0.0001). The data indicate that also in peri-menopausal women, menopausal symptoms evaluated by a validated climacteric scale are associated with biochemical risk factors for atherosclerosis and cardiovascular disease.

1. Introduction

Recent studies indicate that postmenopausal women suffering from disturbances such as hot flushes may be at increased risk for cardiovascular disease. They have a higher BMI [1-3], higher blood pressure [4], increased aortic and artery calcification [5,6], reduced flow-mediated endothelium-dependent vasodilatation [5,6] and a less favorable lipid profile [7]. At the moment it is unclear whether these relations do occur also in women in the peri-menopausal period. This is a period in which clinical disturbances and metabolic changes start to occur, as the consequence of ovarian endocrine modification [8-10]. In one study selectively performed in peri-menopausal women higher vasomotor symptoms were reported to be associated with higher levels of both atherogenic (LDL and triglycerides) and anti-atherogenic (HDL-) lipoproteins [11]. Hot flushes are associated with sleep and mood disturbances [12,13] and these disturbances increase in peri-menopausal women [14,15]. Accordingly, analyses evaluating the bulk of climacteric disturbances are probably more appropriate in determining the impact that these may exert on women's health. Recently, we reported that in postmenopausal women the extent of menopausal disturbances as evaluated by the Greene climacteric scale, is related to endocrine and metabolic modifications possibly leading to an increased cardiovascular risk [16,17]. In this cross-sectional investigation we wanted to evaluate whether the same applies to women in the peri-menopausal period.

2. Methods

Data of women attending the outpatient service for the menopause at our University Hospital in Modena were retrospectively retrieved from an electronic database. Symptomatic but also asymptomatic women that are interested in health prevention attend the service. Once entering in our center, each woman signs a consent form for the anonymous use of her personal data in research. The Institutional Review Board approved the anonymous extraction of the data of interest. Of the 4322 consultations at the Center performed between May 2005 and December 2012, 525 were excluded because women were on hormonal therapy possibly interfering with items evaluated by the Greene climacteric scale (progestins, estrogens or estrogens plus progestins). Of the remaining 3797 consultations, 920 were performed in postmenopausal women, 98 in the reproductive stages below -3 (premenopause) of the STRAW classification (a well recognized although not wholly reliable method to assess different reproductive life stages) [18] and 79 had incomplete data. We used only the data of the entry visit and excluded the 2110 re-evaluations performed on the same subjects. Accordingly, analysis was performed on 590 peri-menopausal women, (reproductive stage -2 and -1 of the STRAW classification),. In these women FSH levels were higher than 30 IU/L and each woman had a period of amenorrhea <12 months.

For each single woman we extracted data such as: age, age at menarche, history of hypertension (no/yes), diabetes (no/yes), smoking behavior (never, past, current), leisure activity (low, moderate, elevated), daily use of wine, beer (no/yes) or daily use of alcoholic beverages (no/yes), use of cholesterol-lowering medicine (no/yes), education level (primary, intermediate; higher; university), height (m), weight (kg), body mass index (BMI; Kg/m2), waist and hip girth, waist/hip ratio, systolic and diastolic blood pressure, fasting levels of glucose, LDL-cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol/HDL-cholesterol, and triglyceride/HDL-cholesterol. The Framingham risk score was calculated on the basis of risk factors for cardiovascular disease [19]. Weight (in kilograms) and height (in meters) reported in the records had been measured while women were wearing light clothes and no shoes. While in standing position, the girths of the women had been measured along the horizontal plane at the level of the natural waist (narrowest abdominal

circumference) and at the level of the hip (maximum extension of the buttocks). Office blood pressure had been measured after at least 10 minutes in a sitting position.

Scores of validated Italian translation of self-administered questionnaires evaluating climacteric symptoms, anxiety and depressive symptoms were retrieved.

The Greene's climacteric scale was used to evaluate climacteric symptoms [20]. The Greene's climacteric scale is composed of 21 items that evaluate vasomotor symptoms (two items), anxiety (six items), depression (five items), somatic symptoms (seven items), and sexuality (one item). For vasomotor symptoms the two questions were "do you suffer from hot flushes?" and "do you suffer from night sweat?". All items have four options that range from not at all (0), a little (1), quite a bit (2), to extremely (3). The sum of items score is used to obtain the Greene climacteric scale score as a whole (range 0-63) or the scores of individual sub-scales for vasomotor symptoms (range, 0 to 6), anxiety (range, 0 to 18), depression (range, 0 to 15), somatic symptoms (range, 0 to 21) and sexuality (range, 0 to 3). Total score and subscales scores were used into the analysis, as numerical data.

The Y-1 form of the State-Trait-Anxiety-Inventory (STAI) was used to further evaluate state of anxiety [21] and the Zung Scale (SDS) to further evaluate depression [22]. These scales are made up of 20 questions with 4 possible answers (score 1-4). Scores range from 20 (best) to 80 (worst).

2.1. Assays

Serum total cholesterol and triglycerides had been measured by enzymatic methods (Olympus AU400, Olympus Diagnostic GmbH, Lismeehan, Ireland), while HDL-cholesterol had been determined after precipitation with PEG 6000. The assay for cholesterol has a sensitivity of 5 mg/dL and a coefficient of variation (CV) of 3%. LDL-cholesterol was calculated accordingly to the Friedewald formula. Glucose had been determined by the glucose oxidase method. This assay has a CV of 1.4%.

2.2. Statistical Analyses

Statistical analyses were performed by the statistical Package Statview 5.0.1 for Apple Macintosh (SAS Institute Inc, Cary, NC, USA1998).

Each single biochemical cardiovascular risk factor such as HDL-cholesterol, LDL–cholesterol, triglycerides, glucose, LDL-cholesterol/HDL-cholesterol ratio the triglyceride/HDL-cholesterol ratio and the ten-year cardiovascular risk by Framingham risk score, as well as, systolic and diastolic blood pressure, was tested by multivariate analysis for its relation to each scale score (SDS, STAI, Greene's and its subscores) along with age, age at menarche, presence of hypertension and diabetes, use of cholesterol-lowering medicine, leisure activity, smoking, level of education, BMI, waist/hip ratio. and FSH values. FSH was used as an indirect index of hypo-estrogenism, more strongly related than any other hormone to stages of menopausal transition and climacteric symptoms [16, 23]. Numerical data were entered into the analyses, as continuous data. Categorical data such as history of hypertension, of diabetes and use of cholesterol lowering medicine were entered into the analysis as single dummy variable, smoking behavior and leisure activity, as two dummy variables, and education as 3 dummy variables. For dummy variables the reference category was the absence of disease, medicine use, smoking, leisure activity or low education. Adjusted regression coefficients of independent determinants were obtained for each cardiovascular risk factor and the ten years cardiovascular risk. For all analyses a p value <0.05 was considered as significant. All results are expressed as mean $\pm$ standard deviation (SD).

3. Results

Enrolled women had a mean age of 49.6±4.0 yr., BMI of 26.2±4.8 and a waist/hip ratio of 0.85±0.09. Ninety-one percent were married or in a long-term stable relationship, and 58.8% with a low grade of education. Among them, 43.5% engaged in leisure activities, 3.6% suffered from diagnosed hypertension and 0.5% suffered from diagnosed diabetes. Wine or beer were used daily by 43.5% of the women, while spirits were used by 1.65% of them. The ten-year probability of cardiovascular disease was 2.25±5.3. The score of the Greene Climacteric scale was 27.3±13.3, of the STAI scale was 47.2±10.0, and of the SDS scale was 38.0±9.9 (Table 1). Women that were excluded for missing data did not differ from analyzed women in any of the parameters considered (data not shown).

Neither STAI nor SDS scores were related independently to any biochemical or biophysical risk factor for cardiovascular disease. Data that were not independently related to any of the cardiovascular risk factor taken into consideration are not presented.

Most cardiovascular risk factors were independently related to BMI and waist/hip ratio (Table 2). On the other hand, multiple regression analysis revealed that also the Greene's Climacteric score and sometimes some of its sub-scores were independently related to most biochemical indexes of cardiovascular disease (Table 2).

When corrected for confounders, along with BMI and waist/hip ratio the Greene's score was a positive determinant of triglycerides (R^2=0.249; p=0.0001), triglycerides/HDL-cholesterol (R^2=0.316; p=0.0001), glucose (R^2=0.101; p=0.0003), and the 10-year risk for cardiovascular disease calculated by the Framingham formula (R^2=0.081; p=0.0001). The Greene's vasomotor sub-score was the only parameter independently related to LDL-cholesterol (R^2=0.025; p=0.01) and along with BMI and waist/hip ratio it was an independent determinant of LDL/HDL-cholesterol (R^2=0.143;p=0.0001). The Greene's depression sub-score was a negative determinant of HDL-cholesterol along with BMI and waist/hip ratio (R^2=0.179; p=0.0001)(Table 2).

The Greene's score or its sub-scores were not determinants of blood pressure values. Positive determinants of systolic blood pressure were (R^2=0.090; p=0.0001) age (β= 0.717; 95% confidence interval (CI) 0.409; 1.025), BMI (β = 0.598; 95% CI 0.335; 0.861), and waist/hip ratio (β =17.1; 95%

CI 2.5;31.8). Positive determinants of diastolic blood pressure were (R^2=0.091; p=0.0001) age (β = 0.377; 95%CI 0.169; 0.584) and BMI (β =0.564; 95% CI 0.387; 0.742).

4. Discussion

The data herein obtained confirm that also in peri-menopausal women the extent of climacteric complaints is associated with an enhanced risk of cardiovascular disease. In women across the menopause hot flushes are directly related to unfavorable metabolic modifications or sub-clinical indexes of cardiovascular disease [1-7]. Hot flushes are related to mood complaints [14,15], and along with them they characterize the bulk of menopausal disturbances. The Greene's climacteric scale is a combination of sub-scales evaluating vasomotor complaints, mood, somatization, and sexuality. Accordingly, it summarizes the burden of climacteric disturbances. The present study was performed in a selected population of perimenopausal women, and it shows that the Greene's scores are related to biochemical cardiovascular risk factors, to the Framingham calculation of the ten years risk of cardiovascular disease and to the triglyceride/HDL-cholesterol ratio. The latter is not included in the Framingham calculation, but it is still considered an independent risk factor for cardiovascular disease [24,25]. Similar data, were obtained, although inconsistently [26], in women mostly in postmenopause [7,16,17], by the evaluation of hot flushes alone.

The association of climacteric symptoms with some cardiovascular risk factors may indicate a general vulnerability of selected women to gonadal steroid fluctuations of the perimenopause. On the other hand, it may also indicate a cause-effect relationship. It is difficult to hypothesize that climacteric symptoms are induced by metabolic abnormalities, but the opposite is possible. An increased catecholaminergic activity (27), and modification in calcitonin-related peptide [28] may represent mechanisms linking hot flushes with an increased cardiovascular risk. In postmenopausal women, we proposed that stressful menopausal symptoms increase cortisol production, and, as the consequence, insulin resistance and alterations of lipid metabolism [16,17]. Present data indicate that this may be true also in peri-menopausal women, where the Greene's scores were related to biochemical modifications clustering in the metabolic syndrome such as decreased HDL, increased triglycerides, and increased glucose.

Blood pressure was not related to the Greene's climacteric score. Data on the association between hot flushes and blood pressure are mixed with some reporting an association [4,7] and others not [29]. It

is possible that for the limited number of the considered subjects, our study failed to find a significant association between climacteric symptoms and blood pressure values.

This study has several limitations. The study was hospital-based and its results could not be applied to the general population. It has a cross-sectional design, which is, by the way, similar to many previously published studies [3-7, 16,17]. The study is based on subjective answers to questions with no objective evaluation. This is particularly true for the Greene's vasomotor scale that was based on two questions testing patient's bother associated with symptoms rather than frequency or severity of the symptoms. Nevertheless, the strength of this study is that it is not limited to hot flushes, a highly specific but single index of climacteric complaints, but instead it presents a more exhaustive evaluation of symptoms experienced by women across the menopausal transition. Furthermore, some confounding, such as the use of any hormone therapy were excluded.

In conclusion, the present study supports the view that menopausal symptoms may be associated with certain biochemical risk factors for cardiovascular disease. The data indicate that these modifications start to occur very early, in the peri-menopause in association with the increase of menopausal complaints. Although, the correlations between the Greene Climacteric scale and the various outcomes account for only 10 to 30% of the variance, they indicate a metabolic change versus an un-favorable condition that may possibly worsen with time. The data reinforce the view of proactively treating climacteric complaints as soon as they present. Likely, an early treatment contributes to prevent unfavorable metabolic modifications, but this possibility has yet to be fully explored.

Declaration of Interest

None of the Authors declared any conflict of interest with this study.

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Table 1. Baseline characteristics (mean±SD) of the study population.

Age (yrs.)	49.6±4.0
BMI (kg/m2)	26.2±4.8
Waist/Hip	0.85±0.09
Blood Pressure systolic (mmHg)	128.4±19.8
Blood Pressure diastolic (mmHg)	77.1±12.8
Waist/Hip	0.85±0.09
HDL-Cholesterol (mmol/l)	1.66±0.41
LDL-Cholesterol (mmol/l)	3.89±1.36
Triglycerides (mmol/l)	1.10±0.59
Glucose (mmol/l)	5.09±0.82
LDL-cholesterol/HDL-Cholesterol	2.25±1.04
Triglycerides/HDL-Cholesterol	0.77±0.57
Ten-Year probability of CVD*	2.25±5.3
State-trait anxiety score (range 20-80)	47.2±10.0
SDS score (range 20-80)	38.0±9.9
Greene's climacteric score (range 0-63)	27.3±13.1
Greene's anxiety sub-score (range 0-18)	6.6±3.9
Greene's depression sub-score (range 0-15)	5.9±3.7
Greene's somatic sub-score (range 0-21)	5.6±4.0
Greene's vasomotor sub-score (range 0-6)	2.6±2.1
Greene's sexuality sub-score (range 0-3)	1.3±1.1

* calculated accordingly to the Framingham formula [20]. CVD=cardiovascular disease

Table 2. Adjusted regression coefficients by multiple regression analysis of independent determinants of each cardiovascular risk factor and of the ten-year risk for cardiovascular disease (CVD).

Risk Factor	Determinant	β coefficient	95% CI
HDL-Cholesterol (mmol/l)			
	Greene depression	-0.029	-0.056; -0.084
	BMI	*-0.025*	*-0.038;-0.013*
	Waist/Hip	*-0.787*	*-1.52; -0.002*
LDL-Cholesterol (mmol/l)			
	Greene vasomotor	0.012	0.001;0.025
LDL-Cholesterol/HDL- Cholesterol			
	Greene vasomotor	0.063	0.002;0.0168
	BMI	*0.042*	*0.008;0.077*
	Waist/Hip	*2.83*	*0.788;4.89*
Triglycerides (mmol/l)			
	Greene total	0.07	0.0004;0.013
	BMI	*0.039*	*0.0021; 0.058*
	Waist/Hip	*2.54*	*1.46;3.61*
Triglycerides/HDL-Cholesterol			
	Greene total	0.06	0.022;0.095
	BMI	*0.032*	*0.016; 0.049*
	Waist/Hip	*2.65*	*1.65;3.64*
Glucose (mmol/l)			
	Greene total	0.011	0.002;0.020
	BMI	*0.033*	*0.006;0.061*
	Waist/Hip	*1.64*	*0.17;3.12*
Ten-Year Risk for CVD			
	Greene total	0.046	0.006;0.087
	BMI	*0.157*	*0.046;0.267*
	Waist/Hip	*13.98*	*7.16;20.8*

Regression models are adjusted for age, age at menarche, presence of hypertension, diabetes, use of cholesterol lowering medicine, smoking, leisure activity, level of education and FSH values. *The Ten-Year risk was calculated by the Framingham formula [19]. In this case the model was not adjusted for age and smoking, because these two parameters are necessary to calculate the ten-year risk.

I declare that I partecipated in the ideation, analysis and writing and that I have seen the final version. I have no conflict of interest

Angelo Cagnacci

I declare that I partecipated in the ideation and clinical management of patients and that I have seen the final version. I have no conflict of interest

Federica Palma

I declare that I partecipated in the ideation and clinical management of patients and that I have seen the final version. I have no conflict of interest

Cecilia Romani

I declare that I partecipated in the ideation and statistical analysis and that I have seen the final version. I have no conflict of interest

Anjeza Xholli

I declare that I partecipated in the ideation, clinical management and writing and that I have seen the final version. I have no conflict of interest

Manuela Bellafronte

I declare that I partecipated in the ideation, statistical analysis and writing and that I have seen the final version. I have no conflict of interest

Costantino di Carlo