Research Article

A comparative study of autonomic function tests in normotensive premenopausal and postmenopausal women

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Abstract

Background: Premenopause is a term that encompasses the entire reproductive period up to final menstrual period, whereas menopause is the permanent cessation of menstruation. Menopause is "burning out of ovaries." After menopause, the primordial follicles become atretic; hence, the ovaries fail completely to produce estrogen. The presence of estrogen receptors in the heart, vascular smooth muscles, and autonomic brainstem centers establishes a probable participation in the regulation of cardiovascular system. **Aims and Objective:** To compare the autonomic function tests in premenopausal and postmenopausal women. **Materials and Methods:** The autonomic function tests in 60 premenopausal women (25–45 years) and 60 postmenopausal women (45–60 years) were compared. The following parameters were studied: (i) body mass index (BMI); (ii) waist–hip ratio (WHR); (iii) Parasympathetic function tests—(a) heart rate response to postural change (30:15 ratio), (b) heart rate variation during deep breathing, and (c) Valsalva maneuver test; and iv) sympathetic function tests—(a) orthostatic tolerance test, (b) sustained isometric handgrip test, and (c) cold pressor test. **Result:** (1) BMI and WHR significantly increased in the postmenopausal women when compared with the premenopausal women. (2) The 30:15 ratio significantly decreased in the postmenopausal women when compared with the premenopausal women whereas heart rate variation during deep breathing and Valsalva maneuver test did not show any significant change. (3) All the sympathetic function test results significantly increased in the postmenopausal women when compared with premenopausal women. **Conclusion:** This finding showed an increased tendency of obesity and autonomic imbalance with sympathetic overactivity in the postmenopausal women when compared with the premenopausal women.

KEY WORDS: Autonomic Function; Postmenopausal Women; Premenopausal Women

Introduction

Menopause is "burning out of ovaries." After menopause, the primordial follicles become atretic; hence, the ovaries fail completely to produce estrogen.[1] Premenopause is a term that encompasses the entire reproductive period up to final menstrual period, whereas menopause is the permanent cessation of menstruation.[2]

There is a combined contribution of obesity, physical inactivity, and changed estrogen metabolism in the disease risk of postmenopausal women.[3] The high incidence of ischemic heart disease after menopause suggests a close association between ovarian hormone levels and cardiovascular system.[4] Autonomic control of heart plays an important role in the cardiac mortality.[5]

The changed sympathovagal activity poses an unfavourable effect on health.[3] Hence, there is a need to understand the

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autonomic changes that take place after the cessation of estrogen secretion, i.e., menopause. So, the objective of this study was to compare the autonomic function tests in premenopausal women in the age group of 25–45 years and postmenopausal women in the age group of 45–60 years.

Early detection of subclinical autonomic dysfunction in postmenopausal women, therefore, will improve the quality of life by proper medication and lifestyle modification.

Material and Methods

This case–control study was done in 60 premenopausal women and 60 postmenopausal women. The subjects were randomly selected from general population around the hospital area. The mean systolic and diastolic blood pressures of the subjects were 110 ± 7.2 and 78 ± 2.1 mm Hg, respectively.

Group 1: Cases (Postmenopausal Women)

The inclusion criteria were postmenopausal women of age 45–60 years with natural cessation of menstruation for 2 years. The exclusion criteria were women on hormone replacement therapy or any other drug that alters cardiovascular function or endocrine function; women with history of hypertension, diabetes, or any systemic or metabolic disorder; women with any history of addiction; trained athlete, or women performing any kind of strenuous exercise, yoga, or meditation.

Group 2: Control (Premenopausal Women)

Women of age 25–45 years with regular menstrual cycle were selected and examined in follicular phase when the hormonal variations are not influenced by progesterone.[5]

The exclusion criteria were women on oral contraceptive pills or any medication that alters cardiovascular function or endocrine function; lactating and pregnant women; women within 2 years of postpartum; trained athlete, or women performing any kind of strenuous exercise, yoga, or meditation.

Procedure

Anthropometry[3]

a. Body weight (kg): A digital weighing scale was used to measure body weight with an accuracy of ±100 g. Subjects were weighed without their shoes.
b. Height (m): The standing body height was measured without shoes to the nearest 0.5 cm with the use of height stand with shoulders in relaxed position and arms hanging freely.
c. Body mass index (BMI) (kg/m^2): BMI was calculated as body weight in kilograms divided by square of body height in meters.
d. Waist/hip ratio (WHR): Waist circumference was measured at the level of iliac crest and hip circumference at the fullest point around buttocks. Waist circumference was divided by hip circumference in order to calculate the WHR. WHR $>$ 0.9 were considered obese subjects.

Determination of resting blood pressure. The blood pressure was measured in lying down position after an initial rest of 15 min.[6] The cuff was placed on subjects right arm, at the heart level, and the blood pressure was measured by palpatory method. The systolic and diastolic blood pressures were recorded by auscultatory method. The systolic blood pressure was defined as the appearance of first Korotkoff sound and diastolic blood pressure as disappearance of phase 5 Korotkoff sound. Two readings were taken at an interval of 30 s. Thereafter, the mean of two readings was taken as the normal blood pressure.

Autonomic function tests. The subjects were made to rest for 15 min in the supine position. The resting time given to subjects in between the two tests was 5 to 10 min.

Parasympathetic function tests

- Heart rate response to postural change (30:15 ratio)[3]: After a complete rest of 15 min in the supine position, the ECG recording was started. The subject was instructed to stand erect from the supine position as quickly as possible (within 3 s) with continuous ECG recording for at least 30 s. The ratio of the longest RR around the 30th beat after standing to the shortest RR interval around the 15th beat after standing were calculated for result of 30:15 ratio: normal, $\geqslant$1.04; abnormal $\leqslant$1.00.
- Heart rate variation during deep breathing[3]: The subject was instructed to take deep inspiration over 5 s and followed by expiration over next 5 s, completing six respiratory cycles in 1 min (six cycles were repeated in 1 min in this test). The mean of the minimum RR intervals in the six inspiratory cycles was calculated and heart rate determined. In addition, the mean of the maximum RR interval in the six expiratory cycles of the same tracing were calculated for heart rate during expiration. The difference of the heart rate between the maximum in the inspiratory cycle and the minimum in the expiratory cycles was calculated and was used as result of the test: normal $\geqslant$ 15 beats/min.
- Valsalva maneuver test[3]: The subject was instructed to exhale forcefully through the mouth piece of a modified mercurial sphygmomanometer and to maintain pressure in the manometer up to 40 mm Hg for 15 s. ECG recordings were taken during the maneuver and continued for about 30 s after the performance. The ratio of the longest RR interval after blowing to the shortest RR interval during blowing was calculated: normal $\geqslant$1.21; abnormal $\leqslant$1.1.

Table 1: Comparison of BMI (kg/m^2) between premenopausal and postmenopausal women.

Groups	Group I (cases)	Group II (control)
Mean	27.4	21.9
± SD	4.47	1.55
Z	4.95	
P	0.01	
Significance	Highly significant	

Table 2: Comparison of WHR between premenopausal and postmenopausal women.

Groups	Group I (cases)	Group II (control)
Mean	0.95	0.79
± SD	0.12	0.06
Z		5.33
P		0.01
Significance	Highly significant	

Sympathetic function tests

- Orthostatic tolerance test[3] (apparatus: mercurial sphygmomanometer and stethoscope): Basal blood pressure was recorded in the spine position by auscultatory method; the subject was asked to stand up, and after 50 s, the blood pressure was recorded. Any change in the blood pressure is determined as the difference between the recording while supine and standing position. A decrease in systolic blood pressure >20 mm Hg and decrease in diastolic blood pressure >10 mm Hg during 1 min suggest autonomic dysfunction.
- Cold pressor test[7]: The subject was asked to immerse the hand in ice cold (4°C) water for 1 min and the blood pressure recorded in supine position by auscultatory method. This maximum blood pressure recording obtained with a hand in 4° C water was taken as an index of response. Normally, both systolic and diastolic blood pressures should increase at least by 10 mm Hg at the end of 1 min of immersion.
- Sustained isometric handgrip (IHG) test[3] (apparatus: mercurial sphygmomanometer, stethoscope, and handgrip dynamometer): The subjects were asked to perform maximum grip of the handgrip dynamometer with their dominant hand, and the maximum capacity was noted down. After 5 min in the sitting position, the subjects were asked to hold their grip with 30% of the maximum capacity for 5 min, and the blood pressure was recorded just after release of the grip. The rise in diastolic blood pressure was calculated and taken as the result of IHG test: normal, 16 mm Hg or more; borderline, 11–15 mm Hg; abnormal, 10 mmHg or less.

Statistical Analysis: All the results were obtained by applying standard error of difference between two means tests (*Z*-test). Before the procedure, a written informed consent was signed by the subjects, as willingness to volunteer in the study.

Results

The BMI and WHR statistically significantly increased in the postmenopausal women in comparison with the premenopausal women. There was a statistically significant decrease in 30:15 ratio, whereas the results of deep breathing test and Valsalva maneuver test did not show any significant change in the postmenopausal women when compared with the premenopausal women. The sympathetic function test results significantly increased in the postmenopausal women when compared with the premenopausal women.

Discussion

In this study, there was a statistically significant increase in BMI in the postmenopausal women when compared with the premenopausal women [Table 1]. Similar significant increase in BMI in the postmenopausal women has been reported by Chaudhuri et al.[3] Estrogen acts on pro-opiomelanocortin (POMC) neurons, regulate their cellular activity through estrogen receptor (ER)α, and suppress food intake.[8] Moreover, estrogen levels are closely associated with leptin levels. Leptin modulates energy balance in the hypothalamus by exerting an anabolic effect and exhibiting a lipolytic effect. Estrogen increases the leptin sensitivity by controlling the expression of leptin-specific receptors. In addition, resistin is a hormone that is produced by adipocytes.[8] After menopause, the ovaries fail completely to produce estrogen,[2] resulting into a deregulation of energy metabolism that may have induced an elevation in the total adiposity in the postmenopausal women.[3]

Because WHR is used to indicate the abdominal fat accumulation[9] and is found to be more predictive than BMI,[3] we compared the WHR of the postmenopausal women with the premenopausal women [Table 2]. There was a statistically significant increase in WHR in the postmenopausal women when compared with the premenopausal women (WHR > 0.9 in women is considered abnormal).[3] Estrogen promotes and maintains the characteristic female type of fat distribution that features the build up of adipose tissue, particularly in the subcutaneous fat depot with only diffident build up of intra-abdominal adipose tissue. Estrogen maintains the fat distribution by enhancing the usage of lipids as energy source and promotes the abdominal fat reduction.[8] Hence, in postmenopausal women, the decline in estrogen results into increase in the abdominal fat, leading to increased WHR.

Table 3: Comparison of parameters of parasympathetic function tests between premenopausal and postmenopausal women.

Tests	Group I (cases)		Group II (control)		Z	P	Result
	Mean	± SD	Mean	± SD			
30:15 ratio	0.09	0.02	1.23	0.16	54.29	<0.01	Significant
Deep breathing test	17	2	16.3	2	1.92	>0.01	Not significant
Valsalva maneuver test	1.29	0.05	1.27	0.07	1.82	>0.01	Not significant

Table 4: Comparison of parameters of sympathetic function tests between premenopausal and postmenopausal women.

Tests	Group I (cases)		Group II (control)		Z	P	Result
	Mean	± SD	Mean	± SD			
Orthostatic tolerance test							
SBP	10.5	2.6	14.5	2.5	8.69	<0.01	Significant
DBP	5.2	0.6	8.6	1.7	14.78	<0.01	Significant
Cold pressor test							
SBP	18.3	2.4	12.6	2.3	13.29	<0.01	Significant
DBP	14.3	2.4	11.1	1.2	9.23	<0.01	Significant
Sustained isometric handgrip exercise test (DBP)	23	1.4	18.4	2.4	12.83	<0.01	Significant

According to our study, there was a statistically significant decrease in the 30:15 ratio, whereas the results of deep breathing test and valsalva maneuver test did not show any significant changes in the postmenopausal women when compared with the premenopausal women [Table 3]. There was a statistically significant increase in the sympathetic function in the postmenopausal women when compared with the premenopausal women [Table 4].

Human obesity is featured by noticeable sympathetic activation. In addition, a raise from the usual body weight of an individual is associated with a decrease in the parasympathetic activity.[3]Tables 1 and 2 suggest that the postmenopausal women are obese when compared with the premenopausal women. This is a contributing factor for autonomic imbalance found in the postmenopausal women.

Mercuro et al.[10] showed that surgical menopause (oophorectomy) resulted in a decrease in the cardiac vagal modulation, leading to a shift toward the sympathetic activity. Saab et al. studied the cardiovascular and neuroendocrine responses to behavioral stressors in the pre- and postmenopausal women. Their result showed exaggerated cardiovascular and neuroendocrine responses in the postmenopausal women and they also linked the mechanism of these influences to estrogen and their hemodynamic effects.[11]

The physiological levels of estrogen account for an increased vagal and lower sympathetic modulation.[12] The decline in the estrogen levels shifts the autonomic balance toward the sympathetic dominance in the postmenopausal women.[5]

As suggested by some studies, estrogen binds to the membrane receptors to stimulate the nitric oxide release from the endothelium. It facilitates calcium efflux and reduces the calcium sensitivity of contractile elements. Thus, estrogen promotes vasodilation.[13,14] Estrogen also increases β-adrenergic receptor sensitivity to catecholamines to promote vasodilation.[13]

Experimental study showed that, in ovarectomized female rats, acute and chronic administration of estrogen increases the cardiovagal baroreflex sensitivity, and this effect is blocked by the administration of ER antagonist to nucleus ambiguous.[13]

Hence, hormone alteration (decline in estrogen level) is responsible for obesity and autonomic imbalance (sympathetic overactivity) in the postmenopausal women when compared with the premenopausal women.

Conclusion

There is an increase in BMI and WHR and increase in the sympathetic function in the postmenopausal women when compared with the premenopausal women. This study suggests that the increased tendency of obesity and decrease in the level of estrogen from premenopausal to postmenopausal status cause shifting of autonomic balance toward sympathetic dominance.

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