ORIGINAL ARTICLE

CARDIOVASCULAR DISEASE RISK IN PRE- AND POSTMENOPAUSAL WOMEN

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Background: Coronary heart disease is an important cause of morbidity and mortality in postmenopausal women. The present study aimed to compare cardiovascular risk factors: blood pressure, alterations in lipid profile and structural changes in heart in pre- and postmenopausal women. **Method:** It was a hospital based study including 41 women selected on basis of menstrual history. After taking detailed history, clinical examination was performed and fasting blood sample was collected for lipid profile and blood sugar estimation. Atherogenic indices like Castelli's Risk Index-I and II, Atherogenic Index of Plasma and Atherogenic Coefficient were calculated from lipid profile values. Cardiac evaluation was done by echocardiography. **Results:** A statistically significant increase in blood pressure in postmenopausal women was observed. A statistically significant increase was also noted in total cholesterol ($p<0.01$), low density lipoprotein ($p<0.02$) and Castelli Risk Index-II ($p<0.04$) in postmenopausal women. An increase in Interventricular Septal Thickness in diastole ($p<0.003$), Left Ventricular Posterior Wall Thickness in diastole ($p<0.0003$), Aortic Diameter ($p<0.01$), Left Atrial Diameter ($p<0.008$), Relative Wall Thickness ($p<0.005$), Left Ventricular Mass ($p<0.004$) and Left Ventricular Mass indexed to body Surface Area ($p<0.002$) and Height$^{2.7}$ ($p<0.001$) was also found to be statistically significant in post menopausal women. **Conclusion:** Menopause leads to dyslipidemia with atherogenic lipid profile with structural changes in left ventricle structure and mass.

Keywords: Menopause, Cardiovascular disease, Risk factors, Echocardiography, Lipid profile

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INTRODUCTION

Menopause is a physiological state with cessation of menstrual cycles due to loss of ovarian function. The average age of menopause is 51 years[1], but the age of natural menopause may vary from 40 to 58 years. It is an important phase in a woman's life associated with physiological, psychological, cultural and social changes. A wide range of symptoms, including hot flashes, sweating, insomnia, depressive mood, vaginal dryness and general discomfort have been reported by postmenopausal women.[2]

Several physiological changes occur in body mass, adipose tissue distribution, lipid profile and hormonal secretions. Together, these subtle changes increase the risk of dyslipidemia, atherosclerosis, hypertension or coronary artery disease (CAD) in postmenopausal state. According to World Health Organization database non-communicable diseases are a leading cause of death globally.[3] Cardiovascular disease risk in females is less as compared to males in younger age group, but it increases in post-menopausal state asymmetrically according to age as compared to males.[4,5] After menopause, CAD is the prime cause of death in women and incidence increases further with increasing age.[6] Post-menopausal women comprise more than 30% of the females affected with cardiovascular diseases in India.[7]

Menopause results in dyslipidemia with a shift towards atherogenic lipid profile due to oestrogen deficiency. Several researchers have reported higher levels of total cholesterol, serum triglycerides and low density lipoproteins (LDL) with decreased levels of protective high density lipoproteins (HDL) in menopausal women.[8] Framingham Study reported that 12-year incidence of myocardial infarction was positively related to the cholesterol concentration and inversely related to the HDL cholesterol concentration in women.[9]

In an experimental study on isolated rat hearts, post-pubertal gonadectomy induced reduction in myocardial contractile function in females, which was reversed after oestrogen replacement but not after progesterone replacement.[10] Such findings are suggestive of oestrogen having direct effects on myocardium. Hence, menopause may be associated with early structural and functional changes in the heart. 2D-echocardiography is a well-established, consistent and a non-invasive investigation for the assessment of cardiac structure and left ventricular function.

Bearing this in mind, the present study aimed at comparing major cardiovascular risk factors including systolic and diastolic blood pressure (SBP and DBP), lipid profile parameters: total cholesterol (TC), triglyceride (TG), low, very low density and high-density lipoprotein (LDL, VLDL and HDL) and atherogenic ratios. Further, echocardiographic parameters helped us in identifying early structural and left ventricular functional changes in the two study groups. This study may help in identifying these changes in the menopausal transition and adopting strategies to improve cardiovascular risk profile in these women.

MATERIAL AND METHODS

Approval of institutional ethics committee was taken. Twenty pre-menopausal (regular menstruation) and 21 postmenopausal women (cessation of menstruation 2

years ago) who came for executive health check-up were taken as participants for the study after taking informed written consent. The study period was one year from August 2013 to July 2014.

Smokers, alcoholics, tobacco chewers, suffering from a major or minor illness, hormonal dysfunction, hypertension, previous history of CVD, coronary artery disease, cardiomyopathy, valvular heart disease, on medications known to affect lipid profile or taking hormone replacement therapy were excluded from the study.

A detailed medical history was taken and subjects were then taken for anthropometric measurements and clinical examination. Blood pressure was measured using a well calibrated mercury sphygmomanometer. Fasting blood sample was taken for blood sugar (FBS) and lipid profile estimation. Atherogenic indices: Castelli Risk Index-I (CRI-I), Castelli Risk Index-II (CRI-II), Atherogenic Index of Plasma (AIP) and Atherogenic Coefficient (AC) were calculated from the lipid profile values[11]. The subjects underwent 2D M-mode echocardiography by a trained cardiologist using a SIEMENS ACUSON S300 machine. In parasternal short axis view Left Ventricular (LV) dimensions: interventricular septal thickness in diastole (IVSTD), LV diameter in end diastole (LVDD), LV diameter in systole (LVDS) and LV posterior wall thickness in diastole (LVPWTD) were measured according to guidelines of American Society of Echocardiography (ASE)[12]. Left ventricular mass (LVM) calculation was done using Devereux's modified American Society of Echocardiography (ASE) cube equation[13]:

$$LVM=0.8\times[1.04\times(LVDD+LVPWTD+IVSTD)^3-LVDD^3]+0.6\ g$$

Relative wall thickness was estimated from the formula[14]:

$$RWT=(IVSTD+LVPWTD)/LVDD)$$

Values were expressed as Mean±SD. Comparison between the two groups was analysed by the Unpaired Student's *t*-test, and $p\leq0.05$ was considered statistically significant.

RESULTS

Mean age of the two groups was significantly different with postmenopausal women older than the pre-menopausal women, and no statistically significant difference in BMI was observed between the two groups. The blood pressures were higher in postmenopausal women. There was no significant difference in FBS (Table-1).

Table-2 shows the comparison between lipid profile and atherogenic ratios in two study groups. The findings revealed significantly higher total cholesterol, LDL and CR-II in postmenopausal women.

Table-3 shows the comparison between echocardiographic parameters and left ventricular mass in both study groups. The significant findings were increased Interventricular Septal Wall Thickness (IVSD), Left Ventricular Posterior Wall Thickness (LVPWD), aorta diameter, left atrial diameter, Relative Wall Thickness (RWT), Left Ventricular Mass (LVM), Left Ventricular Mass Indexed to Body Surface Area (LVM/BSA), Left Ventricular Mass Indexed to Height$^{2.7}$ (LVM/height$^{2.7}$) in postmenopausal women.

Table-1: Demographic characteristics and haemodynamic profile in pre- and postmenopausal women

Variables	Pre-menopausal women (n=20) (Mean±SD)	Postmenopausal women (n=21) (Mean±SD)	*p*
Age (Years)	37.85±5.31	58.29±6.53	0.0001
BMI (Kg/m^2)	27.72±5.47	27.15±5.14	0.74
SBP (mmHg)	121±19.44	137.43±21.51	0.01
DBP (mmHg)	79.6±12.53	87.62±11.86	0.04
PP (mmHg)	41.4±8.66	49.81±12.01	0.01
MAP (mmHg)	93.4±14.62	104.22±14.70	0.02
HR (beats/min)	81.5±3.49	83.05±10.15	0.52
FBS (mg/dl)	96.05±9.81	96.71±32.24	0.93

BMI=Body Mass Index, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, PP=Pulse Pressure, MAP=Mean Arterial Pressure, HR= Heart Rate, FBS=Fasting Blood Sugar

Table-2: Lipid profile and atherogenic indices in Pre-and Postmenopausal women

Variables	Pre-menopausal women (n=20) (Mean±SD)	Postmenopausal women (n=21) (Mean±SD)	*p*
TC (mg/dl)	177.25±32.51	204±34.57	0.01
TG (mg/dl)	124.5±61.39	125.9±78.63	0.95
HDL (mg/dl)	45.70±7.02	46.91±6.62	0.57
LDL (mg/dl)	105.63±29.35	130.54±37.66	0.02
VLDL (mg/dl)	29.03±18.25	25.17±15.7	0.47
AIP	0.39±0.24	0.37±0.24	0.84
AC	2.96±0.97	3.51±1.39	0.07
CR-I	3.96±0.97	4.51±1.39	0.07
CR-II	2.36±0.73	2.93±1.30	0.04

HDL=High Density Lipoproteins, LDL=Low Density Lipoproteins, VLDL=Very Low Density Lipoproteins, AIP=Atherogenic Index of Plasma (Log (TG/HDL), AC=Atherogenic Coefficient (TC–HDL)/HDL), CR-I=Castelli Risk Index-I (TC/HDL), CR-II=Castelli Risk Index-II (LDL/HDL)

Table-3: Echocardiographic parameters and left ventricular mass in pre- and postmenopausal women

Parameters	Pre-menopausal women (n=20) (Mean±SD)	Postmenopausal women (n=21) (Mean±SD)	*p*
IVSD (mm)	10±0.79	11.45±1.97	0.003
LVDD (mm)	41.65±4.48	42.48±3.84	0.53
LVDS (mm)	25.60±2.56	25.19±2.44	0.60
LVPWD (mm)	9.80±0.89	11.50±1.75	0.0003
LVEF (%)	64±0.03	62±0.04	0.10
Aortic Diameter (mm)	22.9±5.80	27.14±4.64	0.01
LAD (mm)	26.85±4.82	30.67±3.93	0.008
LVM (gm)	135.25±28.52	173.20±48.58	0.004
LVM/BSA (gm/m^2)	81.68±16.40	108.35±23.86	0.002
LVM/Ht$^{2.7}$	40.40±9.42	54.55±15.31	0.001
RWT	0.47±0.05	0.55±0.10	0.005

IVSD=Interventricular Septal Wall Thickness, LVDD=Left Ventricular Diameter At End Diastole, LVDS=Left Ventricular Diameter at End Systole, LVPWD=Left Ventricular Posterior Wall Thickness, LVEF=Left Ventricular Ejection Fraction, LAD=Left Atrial Diameter, LVM=Left Ventricular Mass, LVM/BSA=Left Ventricular Mass Indexed to Body Surface Area, LVM/HT$^{2.7}$=Left Ventricular Mass Indexed to Height$^{2.7}$, RWT=Relative Wall Thickness

DISCUSSION

A striking observation of increasing trend of obesity was noted in both study groups as mean BMI was included in obese I category. Urbanization, affluence, changing dietary habits and sedentary lifestyles have been implicated for such findings.[15] A statistically significant difference with higher haemodynamic pressures were noted in the postmenopausal group. Staesson *et al*[16] in their study reported that postmenopausal women had a higher SBP, DBP and PP than pre-menopausal subjects as in the present study also. As postmenopausal women are older in age and age itself is an independent risk factor for hypertension still oestrogen deficiency too has an important role in increased CVD risk. Cardio-protective effects of oestrogen are due to its arterial vasodilatory effect through any of these mechanisms; increased prostacyclin production, calcium channel blockade or endothelium independent vasorelaxation.[17] PP was significantly higher (p<0.01) in postmenopausal women which may be an age related change. A rise in PP is the major cause of the age-related hypertension and arterial stiffness.[18] Pulse wave velocity —an indicator of arterial stiffness is affected in menopause.[19]

In our study, a statistically significant difference was noted in TC and LDL with higher values in postmenopausal women. Similar observations were made by de Kat *et al*[20]. We did not note any remarkable difference between the groups regarding TG and HDL in both groups. Similar observations were made by Ranjit *et al*[21] in their study. Oestrogen deficiency is associated with increase in TC, LDL, and reduction in HDL. The clinical significance of such findings is increased risk of CAD. Raised serum cholesterol and TG concentrations have a positive relationship, and HDL cholesterol has an inverse relationship to the risk of CAD. The cut-off value of CRI-I in healthy individuals is about ≤3.5, and for CRI-II it is about ≤3. We noted significantly higher (p<0.04) CR-II and higher values of CR-I (4.51±1.39) in postmenopausal women, though the difference in CR-I could not attain statistical significance. Nair *et al*[22] in their study noted that individuals who had higher TC/HDL-C ratio when compared with those without raised ratio had a higher prevalence of proximal plaque (62% vs 48%, p=0.04) and significant CAD (19% vs 9%, p=0.009). Cardiovascular risk stratification on the basis of AIP values of -0.3 to 0.1 (associated with low risk), 0.1 to 0.24 (medium risk) and >0.24 (high cardiovascular risk) has been documented.[23] Based on this classification we noted high AIP values in pre-menopausal (0.39±0.24) and postmenopausal (0.37±0.24) women suggestive of both groups having a high risk of CVD.

Structural changes in arterial wall and impairment of endothelium dependent vasodilation due to oestrogen deficiency may result in structural changes in left ventricle. Arterial stiffness without hypertension has been associated with LV remodelling and arterial hypertrophy with cardiac hypertrophy.[24] In the present study we noted statistically significant difference in IVST, LVPWT, RWT and LVM with higher values in postmenopausal women. Duzenli *et al*[25] in their study noted that RWT, IVST and LVPWT, and LVM were significantly higher in postmenopausal women compared to premenopausal women even when age matched subjects were taken up for the study. Schillaci *et al*[26] in their study on normotensive postmenopausal women noted greater RWT and mid-wall fractional shortening. We noted significantly higher aortic diameter (p<0.01) in postmenopausal women. It has been suggested that with ageing as arterial compliance decreases, abdominal aortic diameter increases and is linked with the increase in CAD risk[27]. The altered composition of aortic wall has been implicated for increase in aortic diameter with loss of distensibility and increased wall stress. LAD was noted to be significantly increased in postmenopausal women. This could be a change associated with normal ageing related to increased arterial stiffness which increased LV afterload. Further, the anatomical and haemodynamic perturbations in the LV transmitted to the LA, promoting atrial stretch and dilatation[28]. We noted a significantly higher LVM, LVM indexed to BSA and height$^{2.7}$ in postmenopausal women. Several studies have noted increase in LVM in women which may be due to age, BP, body size and stroke volume. Sex hormones may be another important determinant of LVM[29]. Framingham Study reported that the prevalence of left-ventricular hypertrophy increased with age (p<0.001), with 33% of men and 49% of women age 70 or older showing features of LVH[30].

CONCLUSION

Menopause is a transition phase with several physiological changes which have an impact on cardiovascular health of a woman. Estimation of lipid profile, atherogenic indices and echocardiographic evaluation of structure and function of heart can help us stratify cardiovascular risk factors in postmenopausal women. This can help in instituting corrective measures at the earliest

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