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Menopausal Status and Cardio-metabolic Risk: A cross sectional study from Haryana State, India

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ABSTRACT

Objectives: The study aims to understand the effect of menopause on cardiovascular disease risk factors among the post menopausal women. (Natural and hysterectomy)
Methods: A cross sectional study design was devised in which data relating to demographic, reproductive, anthropometric, physiological and biochemical variables was assessed from 1014 women. The difference in the cardiovascular disease risk factors was ascertained among the participants according to menopausal status. Logistic regression (unadjusted and age adjusted) was utilized to evaluate the association of menopausal status and cardiovascular adversities.
Results: Women with natural menopause and hysterectomy had significantly increased risk for central obesity, dyslipidemia and non HDL cholesterol in both unadjusted and age adjusted models. Increased risk of hypertension and hypertrigyceradem ic waist was documented only among women with a history of natural menopause.
Conclusion: Postmenopausal women had an abnormal cardiometabolic risk profile as compared to premenopausal women most importantly even the younger women with hysterectomy were found to be at an equally increased risk for cardio-metabolic disorders as compared to premenopausal women. The study highlights the increasing epidemic of cardiovascular diseases following menopause. The present study serves as a model for public health policy makers, in identifying women at risk for cardiovascular diseases.

Keywords: Menopause, hysterectomy, cardio-metabolic risk, dyslipidemia, hypertension, anthropometry.

INTRODUCTION

Cardiovascular disease accounts for more than 17 million deaths globally, 80 percent of which occur in low and middle income countries.(WHO 2011)The prevalence of deaths due to non communicable diseases including cardiovascular diseases and diabetes has substantially increased worldwide with a sharp rise being reported from the South Asian countries.(WHO 2008) The American Heart Association 2013 Update reports that the cardiovascular disease risk is higher among women than in men of the same age. The update reports that since 1984, the number of deaths due to cardiovascular diseases has exceeded in females as compared to the males. These findings highlight the importance of studies that need to be undertaken among females to identify the causal risk factors.

Menopause is an obligatory event in the life of a woman that marks the cessation of her reproductive functions. Menopause, be it natural or surgical, has been associated with increased risk of cardiovascular diseases. (Feng et al., 2008; Ingelsson et al., 2011)The findings of the INTERHEART study reported that traditional risk factors accounted for 94 percent of population attributable cardiovascular risk in women as compared to 90 percent in men, highlighting the importance of traditional risk factors in cardiovascular disease risk assessment. (Yusuf et al.,2004) However, there are several studies (Fonseca et al., 2004) that have also argued the importance of non traditional risk factors in assessment of cardiovascular disease risk cannot be ignored.

The relationship between menopause and cardiovascular adversities is known to vary among different populations of the world and the reasons are attributable to differences in their ethnicity, nutritional and lifestyle factors. (Winkleby et al., 1998)The present study attempts to understand the cardiovascular risk profile (with respect to menopausal status) among women belonging to a rural Mendelian population of North India and following a homogenous vegetarian dietary pattern.

METHODS

The present study is a cross sectional population based study. A total of 1014 ever-married North Indian women were considered through random and purposive sampling from Hathin and Hodal blocks of Palwal district , Haryana state. The study was conducted in 15 villages (Madnaka, Jainpur, Khokhiyaka, Rakhota, Janachouli, Badha, Jhaurkhera,

Dhamaka,Nangli, Mitrol, Aurangbad, Srinagar, Gopalgarh, Bhamarikhera and Banchari).Five women were found to be perimenopausal and hence were excluded from the analysis. The age group for the present study was 30-75 years. To ensure a common genetic, ethnic and geographical background the menopausal and premenopausal women were recruited from a single Mendelian population of North India.

The study protocol was approved by the ‘‘Ethical Committee’’ of the Department of Anthropology, University of Delhi. The data were collected after informed written consent from the participants.

Information pertaining to the socio-demographic variables and indicators for reproductive performance were collected using pretested and modified interview schedule. Anthropometric measurements on participants wearing light clothing and without shoes were ascertained. Anthropometer rod was used to ascertain the height of the individuals. Weight was measured in the upright position to the nearest 0.5 kg using a weighing balance.BMI was calculated by dividing weight (kg) by height squared (m^2).Cut offs for BMI were as per designated by World Health Organization 2000. Besides this waist circumference and hip circumference were also taken. Cut offs for waist circumference and waist hip ratio were defined as designated by Ramchandran et al.2003**.** Additionally, skin folds namely biceps, triceps, sub scapular, abdominal, suprailiac, calf and thigh were also measured .

Blood pressure was measured 3 times at the right brachial artery by sphygmomanometer after a 5 minute rest in a seated position before each measurement.The mean of the three readings was used for the analysis.JCN 7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) criteria were used for the evaluation and classification of blood pressure.(Chobanian et al.,2003)Non-High Density Lipoprotein cholesterol (non-HDL-C), value was calculated by subtracting HDL-C from total cholesterol. (Peters 2008) Hypertriglyceradem ic waist was defined according to data from National Health and Nutrition Survey. National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) criteria were used to define Metabolic Syndrome but modified according to the criteria defined by Heng et al, 2005 for Asians. Body fat % was calculated using the equation provided by Goel et al.2009.

Five millilitres of intravenous blood samples were collected after 12 hours of fasting by trained personnel. Blood samples were transported on ice to the Department of Anthropology, University of Delhi and processed for serum and plasma separation within 3 hours of the sample collection. The separated plasma and serum were stored in -80˚C for

further analysis. Glucose and lipid parameters namely triglyceride (TG), total cholesterol (TC) and High Density Lipoprotein cholesterol (HDL-C) were estimated by spectrophotometer technique using the commercially available kits.(Randox Laboratories Ltd.) The levels of low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were computed using Friedwald's and Fredrikson formula .(Roberts 1988)Statistical analysis were done using SPSS 16 Software.(SPSS,Chicago,Illinois).

RESULTS

Table 1: Baseline characteristics of the study population.

	Premenopausal (1)	Natural Menopause(2)	Hysterectomy(3)	p1(1 vs.2) †	p2(1 vs.3) †
Number (%)	562(55.7)	384(38.1)	63(6.2)		
Age at enrolment(in years)	42(37-50)	50(45-60)	45(39-52)	<0.0001	0.068
Illiterate N (%)	352(65.55)	311(84.51)	45(75)	<0.0001	0.141
Agriculturalists N (%)	285(50.71)	171(44.53)	35(55.56)	0.062	0.466
Smokers N (%)	166(30.51)	192(52.75)	34(57.63)	<0.0001	<0.0001

† p value based on chi square test for categorical variables.

Of the 1009 women recruited for the present study, 562(55.7%) were premenopausal, 384(38.1%) experienced natural menopause and 63(6.2%) experienced surgical menopause. Older age, lower literacy and increased incidence of smoking were prevalent among the postmenopausal women as compared to premenopausal women.

Of the selected cardiovascular risk factors, waist circumference, lipid profile and non HDL cholesterol were significantly higher among postmenopausal women (natural and hysterectomy) as compared that to premenopausal women. BMI was found to be relatively higher among postmenopausal women. Systolic and diastolic blood pressure was significantly higher among women with only natural menopause as compared to that of premenopausal women. However, no difference was found between women with

hysterectomy and premenopause with respect to blood pressure. No specific trend with respect to fasting blood glucose and HDL levels was seen between the groups.

Table 2. Distribution of median levels of traditional and non traditional risk factors among premenopausal and postmenopausal (natural and hysterectomy) women

	Premenopausal (1)	Natural menopause (2)	Hysterectomy (3)	p 1 † (1 vs 2)	p 2 † (1 vs 3)
a. Generalized Obesity (BMI) (kg/m^2)	21.35(19.01-24.15)	21.68(18.68-24.39)	21.92(19.89-25.03)	0.903	0.084
b. Abdominal Obesity (Waist Circumference)(cm)	78(70.98-86)	83.8(74.2-92)	82.5(74.7-92)	<0.0001	0.002
c. Blood Pressure					
Systolic Blood Pressure(mm/Hg)	120(110-129.5)	122(112-134)	120(110-130)	<0.0001	<0.0001
Diastolic Blood Pressure(mm/Hg)	80(74-90)	82(78-90)	80(78-86)	<0.0001	0.955
d. Dyslipdemia					
Fasting Blood Glucose(mg/dl)	77.55(68.55-85.96)	78.46(68.65-87.39)	77.24(69.09-84.69)	0.183	0.939
Cholesterol(mg/dl)	162.2(138.7-189.89)	178.99(155.7-211.86)	182.02(162.42-210.08)	<0.0001	<0.0001
Triglyceride(mg/dl)	90.66(67.97-133.47)	111.16(77.26-148.83)	118.62(83.45-167.43)	<0.0001	0.001
High Density Lipoprotein (HDL)(mg/dl)	50.56(41.92-59.68)	51.5(42.4-59.52)	50.24(41.28-64.59)	0.297	0.547
Low Density Lipoprotein (LDL)(mg/dl)	92.84(70.42-113.34)	103.84(81.4-126.48)	108.06(82.44-128.88)	<0.0001	0.014
Very Low Density Lipoprotein (VLDL)(mg/dl)	18.08(13.59-26.62)	22.23(15.45-29.77)	23.72(16.69-33.57)	<0.0001	0.001
e. Non traditional risk factors					
Non HDL-C(mg/dl)	109.64(89.47-135.6)	127.02(103.61-155.39)	131.32(104.76-164.66)	<0.0001	0.001

† p value based on Mann Whitney's test for continuous (non parametric) variables

With respect to BMI, underweight, overweight and obese individuals did not differ between the groups, though overweight and obese women were highest in the natural and surgical menopause group respectively. Women with abnormal waist hip ratio, lipid profile, body fat percent, non HDL cholesterol and hypertriglyceradem ic waist were significantly higher in the postmenopausal group (natural and hysterectomy) as compared to the premenopausal group. Women with abnormal waist circumference, hypertension, pre-hypertension and metabolic

syndrome were significantly higher among natural postmenopausal women but not among those with hysterectomy. Again no specific trend with respect to hyperglycemia and abnormal HDL was seen. Women with hyperglycemia and low HDL levels were highest in the natural menopause and hysterectomy group respectively.

Table 3. Distribution of traditional and non traditional risk factors among premenopausal and postmenopausal (natural and hysterectomy) women

	Premenopausal (1)	Natural menopause (2)	Hysterectomy (3)	p 1 † (1 vs 2)	p 2 † (1 vs 3)
a. BMI					
Underweight(<18.5 kg/m^2)	104(18.71)	84(22.22)	26(42.62)	0.084	0.865
Overweight (23-24.9 kg/m^2)	84(15.11)	63(16.67)	9(14.75)	0.23	0.918
Obese (≥25 kg/m^2)	115(20.68)	81(21.43)	16(26.23)	0.333	0.367
b. Abdominal Obesity					
Waist Circumference(≥80 cm)	253(45.67)	231(60.95)	34(56.67)	<0.0001	0.105
Waist Hip Ratio(<0.8)	424(76.67)	337(88.92)	53(88.33)	<0.0001	0.039
c. Blood Pressure					
Hypertensive(≥140/90mm/Hg)	150(27.37)	142(37.66)	16(26.2)	<0.0001	0.97
d. Blood Glucose and Dyslipidemia					
Hyperglcemia(>110 mg/dl)	22(3.93)	26(6.77)	1(1.61)	0.135	0.263
Cholesterol(>200mg/dl)	102(18.21)	124(32.29)	21(33.27)	<0.0001	0.003
Triglyceride(150mg/dl)	96(17.17)	95(24.74)	20(32.26)	0.004	0.003
High Density Lipoprotein (HDL) (<45mg/dl)	196(35.13)	118(30.97)	24(39.34)	0.185	0.513
Low Density Lipoprotein (LDL) (>130mg/dl)	80(14.5)	89(23.5)	15(24.6)	0.0005	0.03
Very Low Density Lipoprotein (VLDL) (>30mg/dl)	95(16.9)	95(24.7)	20(32.3)	0.003	0.003
e. Non traditional risk factors					
Pre hypertensive(120-139/80-89mm/Hg)	222(40.51)	149(39.52)	26(42.62)	0.06	0.797
Body fat (%)(≥32%)	301(54.23)	233(61.48)	43(70.49)	0.028	0.015
Non HDL-C(≥130mg/dl)	168(30.1)	178(46.7)	32(52.4)	<0.0001	0.0003
Metabolic Syndrome	122(21.71)	113(29.43)	17(26.98)	0.006	0.339
Hypertriglyceridemic Waist(TG≥2mmol/L;WC>80cm)	40(7.18)	57(14.84)	9(14.75)	<0.0001	0.04

† p value based on chi square test for categorical variables

Women with natural menopause and hysterectomy had more than one fold significantly increased risk for central obesity, dyslipidemia and non HDL cholesterol as compared premenopausal women. However, only women with natural menopause had increased risk for hypertension and hyper-triglyceradem ic waist. Neither women with natural

menopause nor those with hysterectomy had risk for abnormal body fat %, pre-hypertension and metabolic syndrome.

Table 4. Crude and Age adjusted odds ratio for traditional and non traditional risk factors.

	Natural Menopause(1)	Hysterectomy (2)	Premenopausal women(3)	P1 † (1 vs 3)	P2 † (2 vs 3)
Traditional Risk Factors					
Waist Hip Ratio					
Unadjusted	2.441(1.675-3.557)	2.304(1.022-5.191)	1.00 (referent)	<0.0001	0.044
Age adjusted	2.226(1.481-3.289)	2.268(1.005-5.123)		<0.0001	0.049
Waist Circumference					
Unadjusted	1.857(1.424-2.422)	1.556(0.909-2.663)	1.00 (referent)	<0.0001	0.107
Age adjusted	1.796(1.351-2.389)	1.502(0.875-2.578)		<0.0001	0.140
Hypercholestrolemia					
Unadjusted	2.141(1.582-2.899)	2.3(1.303-4.059)	1.00 (referent)	<0.0001	0.004
Age adjusted	1.933(1.397-2.676)	2.239(1.265-3.961)		<0.0001	0.006
Hypertriglyceradem ia					
Unadjusted	1.585(1.152-2.182)	2.297(1.291-4.086)	1.00 (referent)	0.005	0.005
Age adjusted	1.485(1.053-2.094)	2.212(1.239-3.949)		0.024	0.007
High LDL					
Unadjusted	1.807(1.292-2.527)	1.92(1.023-3.602)	1.00 (referent)	0.001	0.042
Age adjusted	1.714(1.194-2.461)	1.883(1.001-3.542)		0.004	0.05
High VLDL					
Unadjusted	1.609(1.168-2.216)	2.331(1.31-4.148)	1.00 (referent)	0.003	0.004
Age adjusted	1.503(1.065-2.121)	2.242(1.256-4.005)		0.02	0.006
Hypertension					
Unadjusted	1.937(1.372-2.736)	0.988(0.491-1.989)	1.00 (referent)	<0.0001	0.973
Age adjusted	1.624(1.119-2.357)	0.914(0.450-1.857)		0.011	0.803
Non traditional risk factors					
Pre-hypertension					
Unadjusted	1.374(0.986-1.913)	1.085(0.581-2.024)	1.00 (referent)	0.06	0.798
Age adjusted	1.334(0.935-1.903)	1.063(0.569-1.989)		0.112	0.848
Body Fat%					
Unadjusted	0.89(0.658-1.205)	1.157(0.61-2.197)	1.00 (referent)	0.452	0.655
Age adjusted	0.927(0.669-1.283)	1.131(0.594-2.152)		0.647	0.788
Non HDL-C					
Unadjusted	2.036(1.553-2.668)	2.562(1.502-4.37)	1.00 (referent)	<0.0001	0.001
Age adjusted	1.955(1.461-2.615)	2.508(1.468-4.286)		<0.0001	0.001
Metabolic Syndrome					
Unadjusted	1.504(1.117-2.025)	1.333(0.738-2.408)	1.00 (referent)	0.007	0.341
Age adjusted	1.347(0.978-1.856)	1.269(0.699-2.303)		0.068	0.433
HTGW					
Unadjusted	2.262(1.475-3.467)	2.203(1.028-4.867)	1.00 (referent)	<0.0001	0.046
Age adjusted	1.931(1.216-3.055)	1.984(0.894-4.377)		0.005	0.09

† p value based on Odds Ratio test.

DISCUSSION

The prevalence of hysterectomy in the present study is higher as compared to other studies (Desai et al.,2011)and also the average age of hysterectomy is 41 years which is quite late.(Singh 2012) Additionally, women with hysterectomy had a more abnormal cardiovascular risk profile as compared to premenopausal women in spite of the same age. The average at natural menopause for the studied group is 46 years which is in the normal range (Singh and Arora 2005; Singh 2012) but a more aggravated cardiovascular risk profile is seen among these women.

When obesity component is considered, central obesity seems to be more influenced by menopause rather than general obesity (BMI). Of the central obesity variables, abnormal waist circumference is significantly higher only among those with natural menopause and not among those with hysterectomy. This could be because of the similar age of the premenopausal women and those with hysterectomy. However, waist hip ratio is found to be effected by both natural menopause and hysterectomy. The findings of the present study are in concordance with several other studies (Van Pelt 2001; Lin et al., 2006) that have reported similar findings. This is because with menopause there is a shift in the storage of fat from the gluteal/femoral region to the abdominal depots, due to decrease in the levels of circulating estrogen. (Toth et al., 2001)

Regarding the lipid profile considered for the present study, menopause either natural or through hysterectomy is found to have a substantial contribution in the increase in dyslipidemic status. That is all the lipid variables except HDL are found to be significantly increased in postmenopausal women (natural and those with hysterectomy) as compared to premenopausal women. Similar trend is observed when the distribution of women with abnormal lipids is considered, implying that individual with abnormal lipid are significantly higher among the postmenopausal women as compared to premenopausal women. The findings of the present study are in concordance with other studies (Feng et al., 2008; Anagnostis et al., 2015) with respect to abnormal lipid profile. However, with respect to HDL the findings are in concordance with some (Mathews 1989; Jensen et al., 1990) but not all studies. (Brown et al., 1993; Davis et al., 1994) The findings of the present study suggest a strong association of hysterectomy with dyslipidemia, which is in contradiction with other studies (Mathews et al., 1989; Silverstein et al., 1997) that have suggested no association of cardiovascular risk factors with hysterectomy. But the results of the present study highlight

an increased frequency of dyslipidemia among women with hysterectomy, who have similar age as that of premenopausal women. The increase in the dyslipidemic status following menopause can possibly be attributed to ovarian failure which induces estrogen deficiency. Estrogen is known to exert its effect on lipid metabolism by regulating the levels of the HDL and LDL cholesterol. Estrogen deficiency contributes to decreased activity of hepatic apolipoprotein A and an increase the activity of hepatic lipase. Simultaneously, it also induces a reduction in the activity of LDL receptors, thereby playing an important role in the regulation of the lipid status during menopause. (Tchernof et al., 1996;Medina et al.,2003)

The relationship between menopause and hypertension is a topic of debate with studies reporting conflicting results. (Coylewright et al.,2008) In the present study, the risk of hypertension was increased among women with natural menopause. The results of the present study are consistent with other studies (Zhou et al., 2014) that have concluded an increased risk of hypertension with menopause.

Among the non traditional risk factors considered only non HDL cholesterol was found to be influenced by menopause (natural and hystrectomy). The results are in accordance with a study among Caucasian women that reported significantly increased risk of abnormal non HDL cholesterol among postmenopausal women.(Schaefer et al.,1995) There are no studies that assessed the risk of elevated non HDL cholesterol among women with hysterectomy. However, hypertriglyceridemic waist was influenced only by natural menopause. These findings are in concordance with a study by (Sarrafzadegan et al.,2013) who reported similar findings among post menopausal Iranian women. Contrary to this the risk of body fat percent, pre hypertension and metabolic syndrome were not found to be influenced by hysterectomy or natural menopause. The present study is in negation with other (Guo et al., 1999) that have advocated risk of increased total body fat percent with menopause. Moreover, menopause did not contribute to increased risk of metabolic syndrome in the present study. These results are in non accordance with other studies (Pandey et al., 2010; Eshtiaghi et al.,2010;Jesmin et al.,2013) that have reported contradictory results.

The strong influence of menopause on central obesity and dyslipidemia among the presently studied women is an important matter of concern for public health policy makers. Though women undergo natural menopause at a normal age, but women who undergo hysterectomy at an early age, are prone to cardiovascular diseases during the middle years of their life. Menopause is an indispensable natural phenomenon that is encountered by women

during her lifetime, which is known to increase cardiovascular disease risk and therefore contribute to the cardiovascular epidemic among women.

The major strengths of the present study are that the subjects are drawn from a single Mendelian population from a specific geographic region. Such a study design is likely to match the premenopausal and postmenopausal women for major confounders like ethnicity, geographical variation, nutrition, lifestyle and cultural practices. The relatively larger sample size of both premenopausal and postmenopausal women is another merit of the study.

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