ASSOCIATION OF MENOPAUSE WITH INFLAMMATION-SENSITIVE PROTEIN THE C-REACTIVE PROTEIN AMONG THE INDIAN WOMEN

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ABSTRACT: BACKGROUND: The changes during menopause are associated with cardiovascular risk factors. Since inflammation is believed to have a role in the pathogenesis of cardiovascular events, measurement of markers of inflammation like high sensitivity C - reactive protein hsCRP has been proposed as a method to improve the prediction of the risk of these events. **AIMS:** The aim of the study was to look at the association of menopause with the inflammatory marker hsCRP, in the pathogenesis of cardiovascular events in urban south Indian menopausal women. **SETTING & DESIGN:** 30 pre-menopausal women as a control & 30 post-menopausal women as a subject were, taken from the Medicine OPD, Medical camps, and staff from Dr.B.R.Ambedkar Medical College Hospital and employees from HMT watch factory. **Inclusion criteria**: Normal healthy women & women who had undergone surgical menopause. **Exclusion criteria**: women with a history of chronic infections like liver disease, rheumatoid disease, jaundice, women on oral contraceptives and hormone therapy. Ethical approval was obtained, subjects were briefed about the study protocol and tests, and a written consent was taken. **METHODS AND MATERIAL:** Anthropometry measurements (Height, Weight, Waist/Hip ratio (WHR), Body Mass index (BMI)), CARDIOVASCULAR PARAMETERS: Systolic blood pressure (SBP)and Diastolic blood pressure (DBP), & BIOCHEMICAL PARAMETERS: Hemoglobin (Hbgm. %), Total Leucocyte Count (TLC), Differential Count (DC), hsCRP was estimated and compared for 30 premenopausal women &30 postmenopausal women. **STATISTICAL ANALYSIS:** Chi-square and Fisher exact test, Student t test done using SPSS 11.0 and Systat 8.0, Excel used to generate graphs, tables. **RESULTS:** Mean ±SD (0.68±1.32mg/L) of hsCRP in post-menopausal women was double the Mean± SD (0.34±0.85mg/L) of hsCRP in pre-menopausal women. The post-menopausal women had an elevated hsCRP (>1mg/L) compared to the premenopausal women but not statistically significant. **CONCLUSION:** hsCRP is increased in post-menopausal women indicating a possibly greater cardiovascular risk.

KEY WORDS: Menopause, Premenopausal women, Postmenopausal women, C-reactive protein, hsCRP, cardiovascular risk factors, inflammatory marker.
MeSH TERMS: Menopause, C-reactive protein, hsCRP, cardiovascular risk factors, inflammatory marker.

INTRODUCTION: Cardiovascular disease is one of the leading causes of morbidity and mortality in women worldwide and also in the developing nations like India[1, 2, 3]. For several years the emphasis has been on identifying the risk factors for cardiovascular disease, with targets being early disease detection and where possible its prevention.

The intermediate risk group for cardiovascular disease[4]comprises up to 40% of the population at risk, constituted mainly of women who are older and have attained menopause. Menopause is associated with an increased risk of ischemic heart disease[5] and cerebrovascular

disease, which collectively are the main causes of morbidity and mortality, which is due to cessation of ovarian function and sex hormone deficiency associated with metabolic disorders[6].

In the process of global risk assessment, scores such as the Framingham score, the Prospective Cardiovascular Munster (PROCAM) score, or the European Society of Cardiology Systematic Coronary Risk Evaluation (SCORE), MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study[7] which are derived from multivariate statistical models, are used to detect the at risk patients, who otherwise cannot be identified on the basis of traditional risk factorsalone[6].

This has prompted the search for novel markers of cardiovascular risk to help improve risk prediction. Such markers could be the inflammatorymarkers[8, 9] that enable detection of underlying inflammatory activation for the purpose of assessing cardiovascular risk[10, 11].

C-reactive protein (CRP) an acute-phase reactant, has been added to the Framingham Risk Score as a tool for global assessment of cardiovascular risk[12,13,14].From the available data, the Centers for Disease Control and Prevention and the American Heart Association Scientific Statement on Markers of Inflammation and Cardiovascular Disease has recommended that hsCRP may be measured in asymptomatic people with an intermediate risk of coronary heart disease (Class IIa recommendation)[15]to optimize the global assessment of cardiovascular risk[16].

The present study was under taken to assess the association of the menopause on the Inflammation sensitive protein the hsCRP in predicting the cardiovascular risk among the urban South Indian postmenopausal women, with targets being early disease detection and prevention.

METHODS:

STUDY POPULATION: The study was undertaken in Dr.B.R.Ambedkar Medical College Hospital and HMT Watch factory, Bangalore. Subjects were taken from the Medicine OPD, Medical camps, and staff from Dr.B.R.Ambedkar Medical College Hospital and employees from HMT watch factory.

A total of 60 subjects were taken and divided into two groups:

Group A - 30 pre-menopausal women, who were still having regular menstrual cycles.

Group B - 30 post-menopausal women, with a history of amenorrhea for >12 months, hFSH level >30mlIU/ml.

Inclusion criteria: Normal healthy women & women who had undergone surgical menopause.

Exclusion criteria: women with a history of chronic infections like liver disease, rheumatoid disease, jaundice, women on oral contraceptives and hormone therapy.

Ethical approval was obtained from the institutional ethical committee. All the subjects were briefed about the study protocol and were fully acquainted with the nature of the tests to be performed including any possible risks and gave a written consent.

Anthropometry:

Height, Weight, Waist/Hip ratio (WHR), Body Mass index (BMI) was obtained using standard method.

If WHR >o.8 patient was considered as obese.

Patients were labeled as follows:

Underweight	<18
Normal	18-24.9
Grade I (Overweight)	25-29.9
GradeII (Obese)	30-39.9
GradeIII (Very Obese)	>40

Table1: BMI

CARDIOVASCULAR PARAMETERS: Systolic blood pressure (SBP)and Diastolic blood pressure (DBP) were recorded using Sphygmomanometer and subjects were labeled.

	SBP (mmHg)	DBP (mmHg)
Normal	<120	<80
Pre-Hypertension	120-139	80-89
Stage I Hypertension	140-159	90-990-99
Stage II Hypertension	>160	≥100

Table 2

BIOCHEMICAL PARAMETERS: Hemoglobin (Hbgm. %), Total Leucocyte Count (TLC), Differential Count (DC) were estimated by a cell counter MICRO 60 by a standard method.

Highly Specific C-Reactive protein (hsCRP): Quantia CRP-US was used for ultra-sensitive determination of CRP by turbidometric method using the instrument systronics 625. Kit used: Tulip reagent kit, lot no 605501. The test specimen is mixed with Quanta-CRP-US latex reagent and activation buffer, allowed to react. Presence of CRP forms insoluble complex producing a turbidity, which is measured at wave length between 505-578nm. hsCRP level <1.0mg/L was considered as low risk, 1.0- 3.0mg/L as average risk and >3.0mg/L as high risk for cardiovascular disease. Estimation of hsCRP was done at Central Laboratory, Richmond Circle junction, Bangalore.

HUMANFOLLICALSTIMULATINGHORMONE (hFSH): Chemiluminescent immunoassay (CLIA) was used for the quantitative determination of FSH levels, using assess immunoassay system (Beckman software coulter system); Kit used: Access FSH reagent kit, Lot no 418683.The amount of analyte in the serum sample is determined from the measured light production by means of stored non-linear calibration curve. Sample test results can be reviewed using the sample results screen. hFSH>30mIU/ml is considered as menopause.

STATISTICAL ANALYSIS: Chi-square and Fisher exact test have been used to test the significance of proportions between Pre and Postmenopausal women. Student t test (Independent) has been used to find the significance of hsCRP and hFSH between them.

The statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc.

RESULTS:

ANTHROPOMETRY:

Anthropometry parameters	Pre-menopause (Mean ± SD)	Post-menopause (Mean ± SD)
Age in years	40.80±5.92	52.00±5.68**
Height in meters	1.53±0.05	1.51±0.06*
Weight in kg	58.00±10.81	61.78±9.89
HIP circumference in cm	87.33±24.98	10.47±15.19**
Waist circumference in cm	75.43±24.05	90.45±14.37**
Waist-Hip Ratio	0.84±0.08	0.85±0.05
BMI (kg/m^2)	24.84±4.56	27.29±4.90*

Table 3: Comparison of Anthropometry parameters between Pre and Postmenopausal Women groups

* Significance at 5%, p< .05 ** Significance at 1%, p<0.01

Table 3, depicts the Anthropometry parameter between pre and post-menopausal women. Hip circumference (p=0.001), waist circumference (p=0.000) and WHR (p=0.030) was significantly more in postmenopausal women. Most of the postmenopausal women were overweight.

CARDIOVASCULAR PARAMETERS:

Cardiovascular Parameters	Premenopause (Mean ± SD)	Postmenopause (Mean ± SD)
Systolic Blood Pressure mm Hg	121.70±13.23	122.86±12.66
Diastolic Blood Pressure mm Hg	80.43±10.13	81.67±8.63

Table 4: Comparison of Cardiovascular Parameters between the two groups

* Significance at 5%** Significance at 1%by student t test

Table 4, Systolic blood pressure (p=0.246) and Diastolic blood pressure (p=0.060)showed no changes in the two groups.

BIOCHEMICAL PARAMETERS:

Hematology	Pre-menopause (Mean ± SD)	Post-menopause (Mean ± SD)
Hemoglobin gm.%	11.55±1.46	12.57±1.31**
Total Leucocyte count	7782.76±2096.27	8565.52±1755.47

Table5: Hematology

** Significance at 1%, p<0.007

Table-5, Hb% was increased in the post-menopausal women p<0.007 and TLC (p=0.041).

hsCRP mg/L	(Mean ± SD)	95% CI
Premenopausal women	0.34±0.85	0.30-0.66

Postmenopausal women	0.68±1.32	0.19-1.18

Table 6: hs CRP levels ofPremenopausal &Postmenopausal women

Table-6, hsCRP level in the postmenopausal women is (0.68±1.32mg/L) & (0.34±0.85mg/L) in premenopausal women.

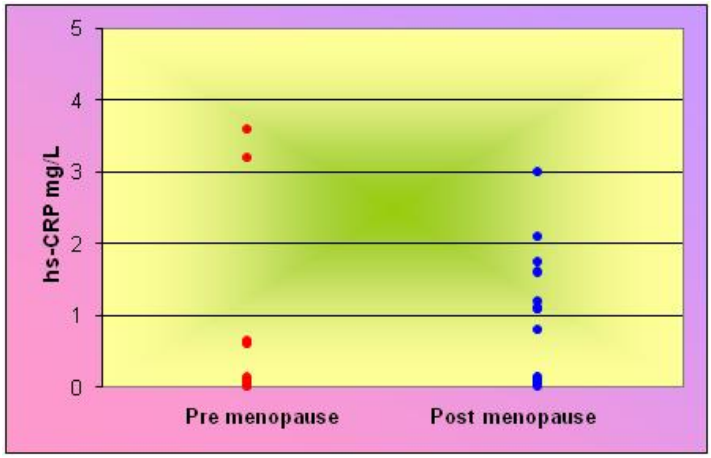
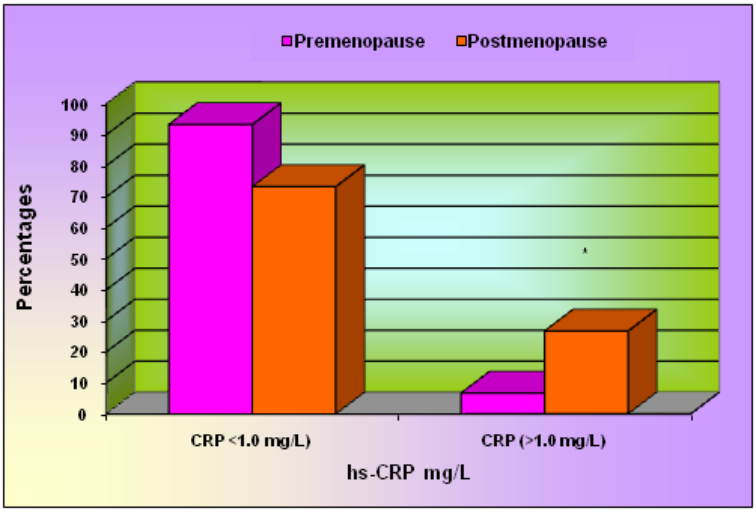


Figure 1

Figure-1:Shows Postmenopausal women have a 4.33 times greater frequency of elevated hsCRP (>1.0mg/L) when compared to Premenopausal women with P=0.038.



P=0.038

Figure 2

Figure -2: Bar diagram shows 26.7% (p=0.038) of postmenopausal women had hsCRP >1.0mg/L compared to 6.7% of premenopausal women.

DISCUSSION: In this cross sectional study, the hsCRP levels were not statistically increased among the post-menopausal women compared to pre-menopausal women. However the frequency of

elevated hsCRP levels (>1.0mg/dl) in post-menopausal women was 4.33 times greater than in Pre-menopausal women. During menopause there is reduction in ovarian function & changes in the concentration of sex hormones, influence levels of inflammatory mediators such as hsCRP. The native CRP binds to oxidized Low density Lipoprotein (LDL) and to partly degraded LDL, causing increase expression of adhesion molecules enhancing the atherogenicity of LDL. This promotes complement activation and thus inflammation in the plaques and it has been claimed that CRP is recognized by a subset of cellular Fcγ receptors and could thereby directly opsonize its ligands and engage multiple processes of inflammation. CRP has also been reported to stimulate tissue factor production by peripheral blood monocytes in vitro and could thereby have important procoagulant effects, increased expression of adhesion molecules, and modulation of Nitric oxide synthesis.

In National Health and Nutrition Examination Survey (NHANES)[17] hsCRP levels increases with age and were noted to be significantly higher among women compared to men[18]. They also found, raised hsCRP levels had the highest cardiovascular risk correlation[16].Sonia Davison et al found that hsCRP is independently associated with increased risk for cardiovascular events in women[9].Rifai N et al in their comparative study of postmenopausal women vs. premenopausal women found increased levels of hsCRP, which were found to be related to increased body fat, notably intra-abdominal fat, and lower insulin-stimulated glucose disposal**.**

The Cynthia et al did not found significant increase in hsCRP levels among postmenopausal women[19].Mark Woodward study correlated that the increased hsCRP in post-menopausal women were due to the deposition of fat due to sedentary lifestyle &estrogen deficiency, because fats are involved in production of inflammatory reactions during which inflammatory mediators like hsCRP are released[20].

Ridkar et al in their prospective study, follow up of women over 3years, hsCRP was found to be the strongest predictor of CVD. So the recent AHA scientific review suggests that monitoring patients for hsCRP may help clinicians identify less obvious patients who are candidates for primary preventive strategies[21, 22, 23].

Data from apparently healthy, middle-aged, postmenopausal women participating in the Women's Health Study hsCRP had the highest cardiovascular risk correlation and added predictive information to the FCRS[24].Importantly, hsCRP differentiated high and low-risk women even among those considered to be at low risk. Among these women, the relative risks of CVD increased progressively in increasing quartiles of hsCRP. Research from the Nurses' Health Study also demonstrates that elevated levels of hsCRP designate heightened risk of CHD.

Ridker et al'scohort study showed that in apparently healthy women at baseline who developed CHD during 8 years of follow-up, hsCRP was a better predictor of CHD than other inflammatory markers in low-risk subgroups[25, 26, 27].

Likewise, results from the multiethnic Atherosclerosis Risk in Communities study show that hsCRP is associated with the development of CHD[23]. Subjects with high hsCRP levels (3 mg/L) were noted to have a greater CHD risk (hazard ratio, 1.72; 95% CI, 1.24 to 2.39) than subjects with average hsCRP levels (1 to 3 mg/L; hazard ratio, 1.31; 95% CI, 0.96 to 1.80). Data from the Reykjavik Study that consisted of almost 30% women also indicate a similar relationship between hsCRP and CHD risk prediction, virtually identical to data in women from the United States.

Adults aged 65 years also found a relationship between hsCRP -3 mg/L and CHD risk that was of similar strength to the Reykjavik data (adjusted relative risk-1.45; 95% CI, 1.14 to 1.86; P-

0.004). However, these older women with elevated hsCRP had high event rates and an estimated CHD risk of 11%, suggesting potential benefit of lowering hsCRP levels[27, 28].In the Rotterdam Study[29], which examined the value of hsCRP in predicting CHD risk in men and women aged 55 years, hsCRP failed to add information to the Framingham risk algorithm[30].

All the above studies infer that, in menopausal women due to the removal of regulatory influence on the inflammatory mediators (hsCRP) due to estrogen deficiency, the incidence of progressive increase in hsCRP has higher chances of developing cardiovascular diseases. The study conducted by the Chennai Urban Rural Epidemiology Study (CURES) showed hsCRP has a strong association with CAD and diabetes.

Though our study did not show a statistically significant increase in levels of hsCRP but 4.33 times increase in frequency of elevated levels of hsCRP among postmenopausal women of South India, signifies their increased risk for cardiovascular diseases similar to Mannino DM et al[31], Rifai N& Ridker PM et al[32], Michelle A. Albert et al[12]& many studies. According to recent AHA suggestion, these women are less obvious patients who are candidates for primary preventive strategies[33, 34, 35].

As our study is cross- sectional in nature, limiting our ability to determine the prolonged effect, ongoing longitudinal studies are needed to assess the relationship between menopause & hsCRP in a larger population.

In conclusion, menopause has an effect on the inflammatory changes that affect the cardiovascular system & hence hsCRP is a useful predictor of the cardiovascular risk.

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