ORIGINAL ARTICLE

# Menopause and metabolic syndrome: A study of 498 urban women from western India

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## ABSTRACT

**Introduction:** Metabolic syndrome (MS) is a cluster of risk factors for future development of type 2 diabetes mellitus and cardiovascular diseases. Menopausal transition with its incidental hormonal changes is considered to contribute to the development of MS. However, age is known to influence MS risk factors.
**Objective:** The present study explores the prevalence of MS in pre- and postmenopausal women from western India.
**Methods:** Four hundred and ninety eight women above 35 years of age, participating in women's health care program were assessed for the prevalence of MS using two criteria- International Diabetes Federation criteria (IDF) and Harmonization (H_MS) criteria.
**Results:** Prevalence of MS amongst postmenopausal women was significantly higher ($P < 0.001$) than that in premenopausal women by both, IDF (premenopausal 45% and postmenopausal 55%) and H_MS criteria (premenopausal 44% and postmenopausal 56%). However, this significance disappeared when data was adjusted for the confounding variable of age.

**Key Words:** International diabetes federation criteria, Indian women, harmonization criteria, menopause, metabolic syndrome

## INTRODUCTION

Metabolic syndrome (MS), a cluster of factors like dysglycemia, dyslipidemia, central obesity and hypertension, is known to pronounce risk for future development of Type 2 diabetes mellitus and cardiovascular diseases (CVD).[1] Studies show that MS and CVD are more common in women above 55 years of age with significant increase in individual risk factors in the postmenopausal phase.[2,3] Changing hormonal milieu with declining estrogen and alteration of its ratio with testosterone has been implicated as a causal factor for the emergence of MS at menopausal transition.[4,5] Besides menopausal hormonal changes, ageing also contributes to clustering of cardio-metabolic risk factors at this time.[6] Hence, there is a debate as to whether the increased incidence occurs due to ageing alone or due to menopausal transitional changes.

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Prevalence of MS has varied greatly in different populations. Prevalence of MS amongst pre-and postmenopausal women has ranged from 13.8% in premenopausal to more than 60% in postmenopausal women.[5,7-17] These differences are probably related to ethnic variations, different criteria used for its definition, study design and sample size. Asian Indians, in general, are prone to have MS at a younger age and have severe morbidity and mortality consequences as compared to Caucasians.[18-20] Recent studies of MS in Indian menopausal women show a prevalence ranging from 19.2% in premenopausal to 32.4% in postmenopausal women.[21] The criteria used to define MS have also been under considerable debate. The earlier criteria used by the National Cholesterol Education Program's

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Adult Treatment Panel III (NCEP-ATP III)[22] were modified in 2005 by including ethnic-specific waist circumference as a measure of visceral obesity to create the International Diabetes Federation (IDF) criteria.[23] However, recently an expert group from the IDF, National Heart, Lung, Blood Institute (NHLBI), World Health Federation and other international associations proposed a harmonized definition (H_MS) that uses uniform cut points for all the risk factors and recommended ethnicity-specific waist circumferences in the criteria for defining MS.[24,25]

The current study was carried out to determine the prevalence of MS and its components in pre- and postmenopausal women (using IDF and Harmonization criteria) and their association with menopausal status.

## MATERIALS AND METHODS

Data were collected retrospectively from 701 women aged 35 to 66 years participating in a women's health checkup program (MAITREYI Comprehensive healthcare program) at our center. Women who were not using hormonal therapy for the past six months were included. The participants were urban women from middle and higher middle class strata residing in the western suburbs of Mumbai and were non-smokers/alcoholics. Participants who had one or more missing values of the risk factors necessary for a diagnosis of MS were excluded. Ultimately, a total of 498 women were included for the present study in examining the prevalence of MS in establishing its relation with MS factors and age . They were divided into two groups: premenopausal and perimenopausal vs. postmenopausal women (as per following definitions: Premenopause - Period during which climacteric women still have menstrual cycles, whether such cycles are regular or not.

Perimenopause or menopausal transition - Period that extends from two years before the last menstruation and until one year later. Women have irregular menstrual cycles and endocrine changes.

Postmenopause - Period that starts one year after the last menstruation. It is subdivided into early (up to five years after the last menstruation) or late (more than five years after the last menstruation).

A predesigned and validated case record form was filled out at the time of registration. This form contained: age, menopausal status (pre or postmenopausal), socioeconomic class, personal and family history, smoking, alcoholism, current medicine intake.

All participants underwent examinations that included interviews for any menopausal symptoms and of MS, CVD. A general, gynecological and systemic examination, including blood pressure measurement and anthropometry (height, weight, abdominal circumference (AC), hip circumference (HC) and Body mass index (BMI)) were performed. Subjects were weighed with light clothes and no footwear and height was measured in centimeters using a stadiometer (Halden). Waist circumference was measured at a level midway between the bottom of the rib cage and superior margin of iliac crests during inspiration and hip circumference at the maximal diameter of the buttocks.

Venous blood was collected in the morning after an overnight fast of 12 h. Blood was collected for complete blood count (CBC), erythrocyte sedimentation rate (ESR), blood glucose, lipids (cholesterol, triglycerides, HDL-C, and LDL-C), serum creatinine and thyroid stimulating hormone (TSH). All women underwent an oral glucose tolerance test using 75 g oral glucose for estimation of blood glucose. After the fasting blood sample was collected 75 g glucose was administered orally and blood collected after 1 and 2 h for blood glucose estimations. The laboratory had internal and external quality control throughout the study.

### Laboratory methods

Total cell count was carried out on the automated cell counter (Sysmex K1000), whereas lipid profiling was carried out by ERBA test kits. Plasma glucose was estimated by Accurex test kit, serum creatinine was done using Ark diagnostics test kits. All biochemical estimations were done using ERBA CHEM PRO instrument. Hormonal tests were done using radio immune assay (DSL kits).

### Statistical analysis

The data were presented as mean, standard deviation, percentages, odds ratios and confidence intervals. Chi-square test was used to establish association between MS and age group, and MS factors.

The baseline characteristics of premenopausal and postmenopausal women were compared using an ANCOVA with age as the covariate. Out of 498 women, 112 who were on antihypertensive medications were excluded from comparison of mean blood pressure and 43 known diabetics were excluded from comparison of mean fasting glucose level while profiling the two groups.

The relationship between the menopausal status and

MS was observed in a simple logistic regression model, with the odds ratio and its confidence interval being estimated at 95%. Bivariate analysis of age group, menopausal status and MS factors has been carried out. Multivariate logistic regression analysis was used to assess the independent contribution of menopausal status to the presence of MS with an adjustment for age (a continuous variable). The analysis was carried out separately for MS with IDF (International Diabetic Forum ) definition and MS with Harmonization Definition (H_MS) and the components considered for IDF and H_MS are given in Table 1. A $P$ value $<0.05$ was considered statistically significant.

## RESULTS

The average age of the study women was 49.8 ± 8.49 years. Out of 498 study women, 274 (55.0%) were premenopausal and 224 (45.0%) were postmenopausal. Baseline characteristics of pre- and postmenopausal women are shown in Table 2.

**Table 1: Components of metabolic syndrome in study women**

| Risk Factors for metabolic syndrome | Value | Additional criteria |
|---|---|---|
| Waist circumference (Central obesity) | ≥ 80cm | |
| Triglycerides | ≥150 mg/dl | Or on treatment for Dyslipidemia |
| HDL-C | <50 mg/dl | Or under treatment for Dyslipidemia |
| Blood Pressure: Systolic BP diastolic BP | >130 mm Hg >85 mm Hg | Or treatment of previously diagnosed hypertension |
| Fasting blood glucose | ≥100 mg/dl | Or previously diagnosed diabetic on treatment |

For IDF criteria: Central obesity with any other two factors
For Harmonization: Any three of the above six factors

Postmenopausal women had significantly higher ($P<0.0001$) mean systolic blood pressure, pulse pressure, total cholesterol, triglycerides and LDL cholesterol and fasting blood sugar ($P<0.01$) than premenopausal women adjusted for age [Table 2].

The Prevalence of MS by IDF criteria was 56.6% (282/498 cases) while by H_MS it was 58.4% (291/498 cases). MS was more prevalent among postmenopausal women than among premenopausal women. According to IDF criteria 55.0% of postmenopausal women had MS compared to 45.0% of premenopausal women with OR=1.166 (CI=.665 to 2.045), $P<.0001$. Similarly, it has been observed that the prevalence of MS according to H_MS criteria was 44% in premenopausal as compared to 56% in postmenopausal women with OR = 1.248 (CI = 0.707 – 2.205) [Table 3].

A statistically significant relationship between increasing age and occurrence of MS ($P<.0001$) was observed. Older women (≥56) were 4.096 (CI: 1.704-9.848) times at risk being diagnosed with MS as compared to younger women less than or equal to 40 years using the IDF criteria and 3.672 (CI: 1.515-8.901) using the H_MS criteria [Table 4].

Results of the multivariate analysis of MS adjusted for age and menopausal status using the IDF and H_MS criteria are given in Table 5. There was a statistically significant relationship between increase in age and prevalence of MS, by both criteria ($P<.0001$). A 4.7 times increase in the risk of MS among women aged

**Table 2: Baseline characteristics of pre- and postmenopausal women participating in the study**

| Variables | Premenopause (274) | | Postmenopause (224) | | Total (498) | | AVCOVA ($P$ value) |
|---|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | Mean | Std. Deviation | Mean | Std. Deviation | |
| Age (years) | 43.87 | 4.33 | 55.91 | 7.58 | 49.28 | 8.49 | <.0001 |
| BMI (Kg/m | 27.23 | 4.51 | 27.70 | 4.70 | 27.45 | 4.60 | <.611 |
| WC | 87.11 | 10.70 | 89.43 | 10.91 | 88.16 | 10.84 | <.251 |
| SYBP* | 122.58 | 14.11 | 131.12 | 18.62 | 125.94 | 16.55 | <.0001 |
| DYBP* | 79.03 | 7.92 | 80.83 | 7.97 | 79.74 | 7.98 | <.024 |
| Pulse pressure* | 43.55 | 10.20 | 50.29 | 13.91 | 46.20 | 12.24 | <.0001 |
| FBS† | 82.54 | 15.31 | 89.44 | 25.70 | 85.51 | 20.70 | <.01 |
| CHO | 195.41 | 36.06 | 213.50 | 37.59 | 203.55 | 37.81 | <.0001 |
| HDL | 48.74 | 11.17 | 49.31 | 11.12 | 48.99 | 11.14 | <.566 |
| TG | 114.01 | 55.25 | 146.55 | 86.06 | 128.64 | 72.54 | <.0001 |
| LDL | 122.70 | 33.93 | 134.39 | 34.81 | 127.95 | 34.78 | <.0001 |

Data are mean ± SD. ANCOVA with age as a covariate. *Of 498 women, 112 on hypertension medications were excluded from comparison of mean blood pressure. †Of 498 women, 43 on diabetic medications were excluded from comparison of mean blood sugar fasting

56-65 (OR: 4.747, CI: 1.914-11.774) compared to those less than 40 years was observed with the IDF criteria and OR 4.045 was observed using the H_MS criteria.

The multivariate analysis of MS (IDF and H_MS criteria) could not show a significant relationship between age-adjusted MS and menopausal status [Table 5] but the risk of MS was found to be more among postmenopausal as compared with premenopausal women.

The prevalence of MS has greatly varied across different studies [Table 6].

National Cholesterol Education Program's Adult Treatment Panel III - NCEP-ATP III, the International Diabetes Federation – IDF, World Health Organization – WHO, Harmonization – H_MS, NA: Not applicable

## DISCUSSION

The prevalence of MS by IDF criteria was 56.6% (282/498 cases) while by the H_MS it was 58.4% (291/498 cases). Use of harmonization criteria resulted in a higher prevalence than with the IDF criteria, though not statistically significant. The prevalence of MS was higher among postmenopausal as compared to premenopausal women in the current study using both IDF and H_MS criteria. In the present study 55 and 56% postmenopausal and 45 and 44 % premenopausal women according to IDF and H_MS criteria respectively were found to have MS. Prevalence of MS was found to be more among older women (56+) as compared to the younger cohort. This finding was statistically significant in both the univariate analysis and multivariate analysis. The higher prevalence of MS in postmenopausal women was not statistically significant after adjustment for age as a confounding variable in the current study.

**Table 3: Prevalence of metabolic syndrome according to IDF and HN criteria by menopausal status**

| | n | IDF criteria | | | | Harmonization criteria (H_MS) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | %MS | OR† | CI 95%† | *P* Value | %MS | OR† | CI 95%† | *P* Value |
| Menopausal status | | | | | <.0001* | | | | <.0001* |
| Premenopause *(ref)* | 274 | 127 (45.0) | 1.000 | | | 128 (44.0) | 1.000 | – | |
| Postmenopause | 224 | 155 (55.0) | 1.166 | 0.665-2.045 | | 163 (56.0) | 1.248 | 0.707-2.205 | |
| Total | 498 | 282 | | | | 291 | | | |

*Chi-square test , †derived from Logit Regression, *ref:* reference category

**Table 4: Prevalence of metabolic syndrome according to IDF and HN criteria by age**

| | | IDF criteria | | | | Harmonization criteria (H_MS) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | %MS | OR† | CI 95%† | *P* Value | %MS | OR† | CI 95%† | *P* Value |
| Age group (years) | | | | | <.0001* | | | | <.0001* |
| ≤40 *(ref)* | 66 | 23 (34.8) | 1.000 | – | | 27 (40.9) | 1.000 | – | |
| 41-45 | 124 | 47 (37.9) | 1.127 | 0.603-2.105 | | 44 (35.5) | 0.780 | 0.422-1.443 | |
| 46-50 | 126 | 83 (65.9) | 3.394 | 1.747-6592 | | 83 (65.1) | 2.465 | 1.285-4.728 | |
| 51-55 | 86 | 60 (69.8) | 3.830 | 1.705-8.602 | | 60 (69.8) | 3.769 | 1.663-8.545 | |
| ≥ 56 | 96 | 69 (71.9) | 4.096 | 1.704-9.848 | | 69 (71.9) | 3.672 | 1.515-8.901 | |

*Chi-square test , † derived from Logit Regression, *ref:* reference category

**Table 5: Multivariate analysis of MS (IDF, Harmonization criteria) adjusted for age, menopausal status among study women**

| Age group and menopausal status | IDF criteria | | | Harmonization criteria (H_MS) | | |
|---|---|---|---|---|---|---|
| | OR | CI 95% | *P* Value | OR | CI 95% | *P* Value |
| Age group (years) | | | .0001 | | | .0001 |
| <=40*(ref)* | 1 | 0.670-2.546 | | 1 | 0.449-1.645 | |
| 41-45 | 1.306 | 1.944-7.956 | | 0.859 | 1.370-5.380 | |
| 46-50 | 3.933 | 1.911-10.310 | | 2.715 | 1.784-9.662 | |
| 51-55 | 4.439 | 1.914-11.774 | | 4.151 | 1.629-10.045 | |
| 56-65 | 4.747 | | | 4.045 | | |
| Menopausal status | | | 0.591 | | | 0.445 |
| Premenopause *(ref)* | 1 | 0.655-2.045 | | 1 | 0.707-2.205 | |
| Postmenopause | 1.166 | | | 1.248 | | |

**Table 6: Prevalence of MS in various studies[5,7-17]**

| Author, year | Country, number of subjects (n) | Criteria for MS | Prevalence of MS according to menopausal status (%) | | |
|---|---|---|---|---|---|
| | | | Premenopausal | Perimenopausal | Postmenopausal |
| Hidalgo LA, 2006 | Equador, 325 | NCEP III (ATP III) | NA | NA | 41.5 |
| Piche ME, 2006 | Canada, 108 | WHO | NA | NA | 29.6 |
| Kim HM, 2007 | Korea, 2671 | NCEP III (ATP III) | 13.8 | NA | 54.6 |
| Ainy E, 2007 | Tehran, 2183 | NCEP III (ATP III) | 53 | 54 | 69 |
| Deibert P, 2007 | Germany, 76 | NCEP III (ATP III) | 23 | NA | 42 |
| Janssen I, 2008 | U.S., 949 | NCEP III (ATP III) | NA | NA | 13.7 |
| Eshtiaghi R, 2009 | Iran, 940 | NCEP III, (ATP III) | 18.3 | NA | 53.5 |
| Figueiredo Neto JA, 2010 | Brazil, 323 | NCEP III<br>IDF | 24<br>44 | NA<br>NA | 37<br>61.5 |
| Indhavivadhana S, 2010 | Thailand, 971 | NCEP III (ATP III) | NA | 12.4 | 16.9<br>19.7 (surgical menopause) |
| Heidari R, 2010 | Iran, 1596 | NCEP III (ATP III) | 44.9 | 57.9 | 64.3 |
| Ruan X, 2010 | China, 181 | | NA | NA | 33.7 |
| Tandon VR, 2010 | India, 500 | NCEP III (ATP III) | NA | NA | 13 |
| Current study | India, 498 | IDF,<br>H_MS | 45<br>44 | NA<br>NA | 55<br>56 |

The prevalence of MS has greatly varied across different studies as shown in Table 6 (vide supra). Differences in socio-environmental and genetic factors, lifestyles, type of menopause (natural/surgical), time since menopause and criteria used for defining MS could be some of the reasons for this variability. The prevalence of MS in premenopausal women varied from 13.8% in a study from Korea to 46.4% in the present study. In another study from India, a prevalence of 22.2% in the premenopausal as compared to 32.42% in the postmenopausal group was reported.[21] In the Santiniketan women study, 214 women were studied for clustering of cardio-metabolic risk factors which were found to be higher in the postmenopause phase.[26] Though all studies for the prevalence of MS in menopausal women have shown a higher percentage of MS in postmenopausal as compared to premenopausal women, most have been cross-sectional. Heidari *et al.*, in a study of 1596 women showed a prevalence of 44.9%, 57.9% and 64.3% in pre-, peri- and postmenopausal women respectively.[15] Janssen *et al.*, in the Study of Women's Health Across the Nation (SWAN), followed 949 premenopausal women over nine years.[5] By the final menstrual cycle, a 13.7% incidence of new-onset MS was observed with an odds ratio of 1.45 (95% CI 1.35–1.56) of developing MS/year in the perimenopausal years. The authors attributed this to progressive androgenization rather than decline in estrogen levels during the climacteric transition.

In the current study, the prevalence of MS was found to be more among older women (≥51 years, OR 4.439, CI 95% 1.914-11.774) as compared to the younger cohort. This finding was statistically significant in both the univariate analysis and multivariate analysis. Women in the higher age group had a statistically significant higher prevalence of MS when adjusted for age and menopausal status with both criteria (IDF and HN ). Though there was a higher prevalence of MS among postmenopausal women when both criteria were considered, this difference was not statistically significant after the adjustment for age. There is current controversy on whether MS worsens with age alone or as a result of the menopausal transition. The Framingham cohort demonstrated fourfold increase in the incidence of CVD in the postmenopausal phase.[27] Women with either surgical or early menopause have also been shown to have a higher CVD risk.[28] However, all studies do not show causal effects of menopause and attribute the increased prevalence of MS in postmenopausal period to ageing. In a cross-sectional study from Brazil, though the prevalence of MS was higher in the post-menopause women, the effect was not statistically significant and ageing was the chief factor for the increase.[13] It is

important to recognize that premature cardiovascular morbidity and mortality are higher in Asian Indians in general.[29] The first myocardial infarction (MI) attack occurs in 4.4% of Asian women and 9.7% of men at age less than 40 years, which is 2- to 3.5-fold higher than in the West European population.[30] In the present study, though OR for MS increased with advancing age, younger women between 40–45 years also had a 35-40% prevalence of MS [Table 4]. Hence against the background of high CVD risk factors in Indian women, it would be important to follow up women of this age group as they transit into menopause to actually determine the influence of changing hormonal milieu on MS.

In conclusion the present study shows a high prevalence of MS amongst women above 35 years of age. Though the prevalence was more amongst postmenopausal women, the significance disappeared when adjusted for age. The cross-sectional nature of our study may be a limitation to show the effect of menopause on the prevalence of MS. Selection bias due to urban women from higher socioeconomic class participating in the healthcare program and the exclusion of ineligible women may be other limitations to generalize the findings to Indian women.

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