ORIGINAL ARTICLE

Correlation of Menopausal Symptoms with Serum Estradiol: A Study in Urban Indian Postmenopausal Women

Renuka Malik[1] · Chanderkala Pokeria[1] · Swati Singh[1]

Abstract

Background Menopause is a hypoestrogenic state. Menopausal symptoms like hot flushes, depression, joint pains and urinary symptoms all correlate with falling estrogen levels.

Material and Methods Four hundred postmenopausal women who underwent natural menopause were included in the study conducted from Nov 2018 to March 2020. Surgical menopause, premature menopause and those on hormone replacement were excluded. Serum estradiol was measured and assessment of severity of menopausal symptoms was done using MRS questionnaire. MRS score of 0–4, 5–8, 9–15 and more than 16 were taken as none/minimal, mild, moderate and severe postmenopausal symptoms, respectively. Correlation between serum estradiol and symptoms was analyzed statistically.

Results Mean age of menopause in our study population was found to be 47.2 ± 3.96 years. Somatic symptoms were found maximum out of all 3 subscales in study population. Psychological subscale which included depression and mood changes was found to have the strongest correlation with serum estradiol level compared to other two subscales (somatic and genito-urinary).

Discussion Psychological symptoms, somatic symptoms and genitor urinary symptoms at menopause show correlation with falling estrogen levels. We found maximum correlation of psychological symptoms with low serum estradiol level.

Conclusion There is an inverse correlation of serum estradiol value with menopausal symptoms, with psychological symptoms (depression, anxiety, mood changes) showing highest correlation with low estrogen levels.

Keywords Serum estradiol · Menopause · Menopausal symptoms · Menopause rating score · Menopause in Indian women

Introduction

Menopause is a retrospective clinical diagnosis following 12 months of FMP (final menstrual period) [1]. Menopause is a hypoestrogenic state. Estrogen receptors are found all over human body brain, heart, skin, bones and urogenital system. Menopausal syndrome comprises of vasomotor symptoms, psychological symptoms and genito-urinary symptoms.

These symptoms apart from hot flushes are also associated with normal aging process. Correlation between these symptoms and declining serum estradiol level is sought in this study.

Material and Methods

The study was carried out at A.V.I.M.S and Dr RML from November 2018 to March 2020. In total, 400 menopausal women attending gynecological OPD who had attained natural menopause were included in the study. Patients with surgical menopause, premature ovarian failure and patients on hormonal replacement therapy were excluded. Patient's age at menopause, duration of menopause and comorbidities were noted.

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Patients were given MRS questionnaire in English and Hindi depending upon their language proficiency, which was filled by the patient in the presence of the researcher.

The postmenopausal symptoms were graded according to the severity. MRS consists of a list of 11 symptoms which are divided into 3 subscales—*Somatic subscale* (hot flashes, heart discomfort, sleep disorder, joint and muscular discomfort) corresponding to questions 1, 2, 3 and 11, respectively, *Psychological subscale* (depressive mood, irritability, anxiety, physical and mental exhaustion) corresponding to questions 4, 5, 6 and 7, respectively, and *Urogenital subscale* (sexual problems, bladder problems, dryness of vagina). Corresponding to questions 8, 9 and 10, respectively, patients graded their symptoms in a 5-point (0–4) Likert scale as none (0), mild (1), moderate (2), severe (3) and very severe as 4 (Table 1). Score were added and individual subscale and total menopausal score calculated and graded. The total score varied from 0 to 44. 0–4 was graded as none or minimal menopausal symptoms, 5–8 as mild menopausal symptoms, 9–15 as moderate and 16–44 as severe postmenopausal symptoms.

After assessment of symptoms detailed physical and gynecological examination was done, and 1 ml blood was withdrawn from median cubital vein for serum estradiol. Serum estradiol was measured using an direct immunoassay Ortho-Clinical Diagnostics' Vitros assay, and results were expressed in units of pMol/L [pMol/L (pg/ml × 3.67)]. The laboratory reference value was below 141 pMol/L for menopausal patients. The severity of menopausal symptoms was then correlated with serum estradiol level.

Statistical Analysis

Categorical variables were presented in number and percentage (%), and continuous variables will be presented as mean ± SD and median. Normality of data was tested by Kolmogorov–Smirnov test. Quantitative variables were compared using unpaired t test/Mann–Whitney test between the patients with and without symptoms, and Pearson's test

Table 1. Menopausal rating scale

Which of the following symptoms apply to you at this time?

(X ONE Box For EACH Symptom) For Symptoms That Do Not Apply, Please Mark "None").

Symptoms:	none	mild	moderate	severe	extremely severe
Score =	0	1	2	3	4
1. Hot flashes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restlessness, feeling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

was used for comparison between severity of complaints. Qualitative variables were compared using Chi-square test/Fisher's exact test. A *p* value of < 0.05 was considered statistically significant. The data were analyzed using Statistical Package for Social Sciences (SPSS) version 21.0.

Observation and Results

Demographic Characteristics of Study Population

Out of 400 postmenopausal women, 33% were in the age group of 40–50 years, 45% were in the age group of 51–60 years, 18.75% were in the age group of 61–70 years, and 3% were in the age group of 71–80 years. Maximum patients were in the age group of 51–60 years.

Age at Menopause: Mean age of menopause in our study population was 47.5 years.

Duration of Menopause: Among our study subjects 71.25% were menopausal since 10 years, 23.75% were menopausal since 11–20 years, 4.25% were menopausal since 21–30 years, and 0.75% were menopausal for more than 30 years.

BMI: About 51.50% had normal BMI, 39.75% were overweight, 8% were obese, and 0.75% were underweight

Associated Comorbidities: In our study of 22.50% women had associated comorbidities, among which 10.75%, had hypertension, 9.50% had hypothyroidism, and 7.75% were diabetic. Rest other comorbidities were 3%.

Common Menopausal Symptoms: In our study, the most common menopausal symptoms reported were joint and muscle discomfort in 67.25% followed by sleep disorders in 65.25%, physical and mental exhaustion was reported in 63.75% menopausal women, vaginal dryness in 59.5%, depressive mood in 55.25%, hot flushes in 53.5, irritability in 50.5%, sexual problems in 42.25%, bladder problems in 39.75%, heart discomfort in 34.5% and anxiety in 19.25% (Table 2).

Severity of Menopausal Symptom: Severity of symptoms experienced in descending order was joint pains (44.25%), hot flushes (34%), sleep disturbance (30.25%), physical and mental exhaustion (30%), depression (22.75%), vaginal dryness (22.50%), bladder problems (14.25%), sexual problems (14%), irritability (11.50%), heart discomfort (8.4%) and anxiety (2.75%). The very severe (score 4) symptom reported among postmenopausal women was joint pain (25.25%), followed by sleep disorders (20.25%), hot flushes in 17%, physical and mental exhaustion in 12.25%, depressive mood (11%), dryness of vagina (8%), heart discomfort (5.75%), bladder problems (5.25%), irritability (4.75%), sexual problems ($n = 16$) 4% and anxiety ($n = 6$) 1.50% (Table 3).

Correlation of Symptoms with Age

Symptom of hot flushes decreased with age, being 81.82% at menopause decreasing to 53.59% at 51–60 years, 10.67% at 61–70 years and further reducing to 8.33% at 71–80 years (Fig. 1).

Joint and muscular pains increased with age which showed a high statistical significance. Bladder problems, sexual problems and dryness of vagina increased with age (Table 2). The severity of menopausal symptoms was maximum in age group of 40–60 years. There was no correlation seen between total MRS score and age of patient ($p = 0.327$) using Fisher test.

Table 2 Prevalence of symptoms and correlation with age

Menopausal symptoms and severity according to menopausal rating scale	40–50 ($n = 132$)	51–60 ($n = 181$)	61–70 ($n = 75$)	71–80 ($n = 12$)	Total	*P* value	Test performed
Hot flushes sweating	108 (81.82%)	97 (53.59%)	8 (10.67%)	1 (8.33%)	214 (53.50%)	< .0001	Chi-square test, 107.703
Heart discomfort	37 (28.03%)	68 (37.57%)	28 (37.33%)	5 (41.67%)	138 (34.50%)	0.291	Chi-square test, 3.739
Sleep problems	84 (63.64%)	116 (64.09%)	53 (70.67%)	8 (66.67%)	261 (65.25%)	0.743	Chi-square test, 1.24
Joint and muscular discomfort	63 (47.73%)	125 (69.06%)	70 (93.33%)	11 (91.67%)	269 (67.25%)	< .0001	Chi-square test, 49.528
Depressive mood	77 (58.33%)	100 (55.25%)	38 (50.67%)	6 (50%)	221 (55.25%)	0.734	Chi-square test, 1.279
Irritability	65 (49.24%)	92 (50.83%)	39 (52%)	6 (50%)	202 (50.50%)	0.984	Chi-square test, 0.16
Anxiety	27 (20.45%)	38 (20.99%)	11 (14.67%)	1 (8.33%)	77 (19.25%)	0.492	Chi-square test, 2.411
Physical and mental exhaustion	77 (58.33%)	121 (66.85%)	49 (65.33%)	8 (66.67%)	255 (63.75%)	0.466	Chi-square test, 2.555
Sexual problems	77 (58.33%)	77 (42.54%)	14 (18.67%)	1 (8.33%)	169 (42.25%)	< .0001	Chi-square test, 36.754
Bladder problems	43 (32.58%)	65 (35.91%)	46 (61.33%)	5 (41.67%)	159 (39.75%)	0.0003	Chi-square test, 18.557
Dryness of vagina	74 (56.06%)	101 (55.80%)	53 (70.67%)	10 (83.33%)	238 (59.50%)	0.039	Chi-square test, 8.385

Table 3 Severity of subscales of menopausal symptoms in study population

Menopausal symptoms	None	Mild	Moderate	Severe	Very severe
Somatic subscale					
Hot flushes sweating	186 (46.50%)	16 (4.00%)	62 (15.50%)	68 (17.00%)	68 (17.00%)
Heart discomfort	262 (65.50%)	67 (16.75%)	37 (9.25%)	11 (2.75%)	23 (5.75%)
Sleep problems	139 (34.75%)	61 (15.25%)	79 (19.75%)	40 (10.00%)	81 (20.25%)
Joint and muscular discomfort	131 (32.75%)	37 (9.25%)	55 (13.75%)	76 (19.00%)	101 (25.25%)
Psychological subscale					
Depressive mood	179 (44.75%)	60 (15.00%)	70 (17.50%)	47 (11.75%)	44 (11.00%)
Irritability	198 (49.50%)	80 (20.00%)	76 (19.00%)	27 (6.75%)	19 (4.75%)
Anxiety	323 (80.75%)	44 (11.00%)	22 (5.50%)	5 (1.25%)	6 (1.50%)
Physical and mental exhaustion	145 (36.25%)	46 (11.50%)	89 (22.25%)	71 (17.75%)	49 (12.25%)
Genito-urinary subscale					
Sexual problems	231 (57.75%)	42 (10.50%)	67 (16.75%)	44 (11.00%)	16 (4.00%)
Bladder problems	241 (60.25%)	55 (13.75%)	47 (11.75%)	36 (9.00%)	21 (5.25%)
Dryness of vagina	162 (40.50%)	63 (15.75%)	85 (21.25%)	58 (14.50%)	32 (8.00%)
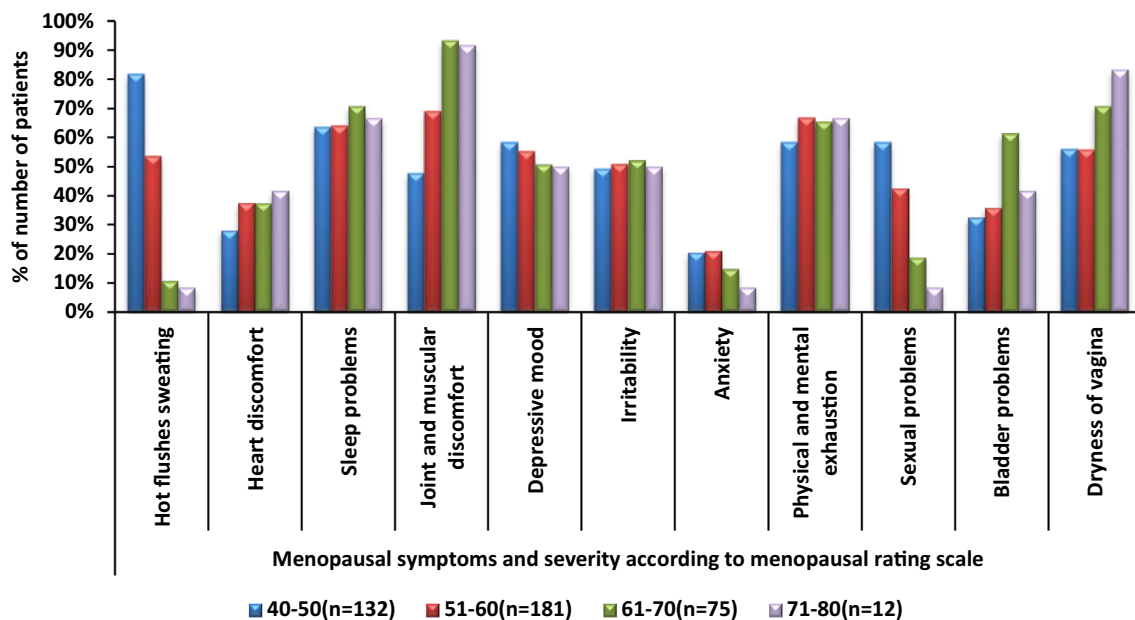
Fig. 1 Correlation of severity of menopausal symptoms with age

Serum Estradiol in Menopausal Women

The range of serum estradiol found in our study was from 5 to 256 pMol/L. The mean serum estradiol of study population was 77.23 ± 39.35 pMol/L with median 78 pMol/L. Serum estradiol in postmenopausal women, reference value of our laboratory was less than 141 pMol/L.

We had 19 patients out of 400 (5.25%) showing higher than expected serum estradiol values. The age of these patients was from 46 to 60 years with mean of 56.9 years, duration of menopause was from 1 to 20 years with mean of 8.8 years, mean BMI 22.3 (21–32) and MRS score varied from 0 to 20, 2 patients having no symptoms.

Correlation of Serum Estradiol with MRS Score

Correlation between serum Estradiol and severity of menopausal symptoms showed statistical significance ($p \leq 0.001$). It was found that with increase in total MRS score there

is decrease in serum estradiol value (using Kruskal–Wallis test) (Table 4, Fig. 2).

The correlation coefficient of somatic symptoms, psychological symptoms, genito-urinary symptoms and MRS score with serum estradiol level showed significant inverse correlation (p value < 0.001). As the serum estradiol level decreases, psychological symptoms (correlation coefficient − 0.619) will increase more as compared to somatic symptoms (correlation coefficient − 0.532) and genito-urinary symptoms (correlation coefficient − 0.495).

Correlation of Serum Estradiol with Somatic Symptoms

There is negative correlation between somatic symptoms and serum estradiol level (Fig. 3). The correlation of serum estradiol and hot flushes is of statistical significance ($p < 0.002$). The correlation of serum estradiol and joint and muscular discomfort is of statistical significance ($p < 0.002$). The correlation of serum estradiol and sleep problems is of statistical significance ($p < 0.001$).

Correlation of Serum Estradiol with Psychological Symptoms

There is negative correlation between the psychological symptoms and serum estradiol level (Fig. 3). The correlation

of serum estradiol and depressive mood is of statistical significance ($p < 0.001$). The correlation of serum estradiol and physical and mental exhaustion is of statistical significance ($p < 0.001$).

Correlation of Serum Estradiol with Genito-Urinary Symptoms

There is negative correlation between genito-urinary symptom score with serum estradiol level. Higher the score of genito-urinary symptoms lower the value of serum estradiol level (Fig. 3). The correlation of serum estradiol and sexual problems is of high statistical significance ($p < 0.003$). The correlation of serum estradiol and bladder problems is of high statistical significance ($p < 0.001$). The correlation between serum estradiol and vaginal dryness had high statistical significance ($p < 0.001$).

Discussion

Menopause is a hypoestrogenic manifestation of a variety of symptoms following cessation of ovarian function so distinct from aging, though a part of aging process. During reproductive years, estrogen synthesis begins in theca cells in ovary with androgen synthesis and ends with conversion of androgens to estrogens in granulosa cells by the enzyme

Table 4 Correlation of serum estradiol (pMol/L) with total MRS score

Serum estradiol (pMol/L)	0–4{None} ($n=34$)	5–8{Mild} ($n=85$)	9–15{Moderate} ($n=154$)	≥ 16{Severe} ($n=127$)	Total	P value	Test performed
Mean ± SD	116.04 ± 37.74	103.61 ± 28	79.64 ± 32.56	46.26 ± 29.53	77.23 ± 39.35	< .0001	Kruskal Wallis test; Chi-square = 163.208
Median (IQR)	110 (89.475–144.525)	103 (89–123)	78 (57–96.525)	40 (24.2–59)	78 (45.925–101.775)		
Range	29–194	20–167	28–256	5–160	5–256		

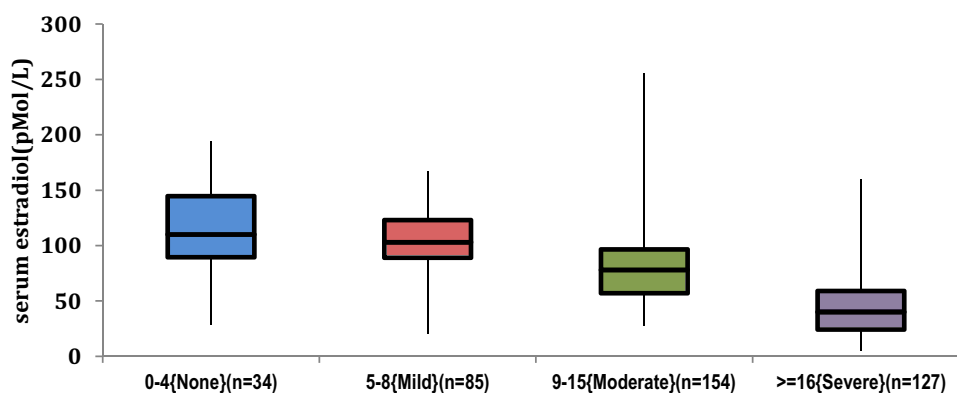**Fig. 2** Correlation of serum estradiol (pMol/L) with menopausal symptoms score
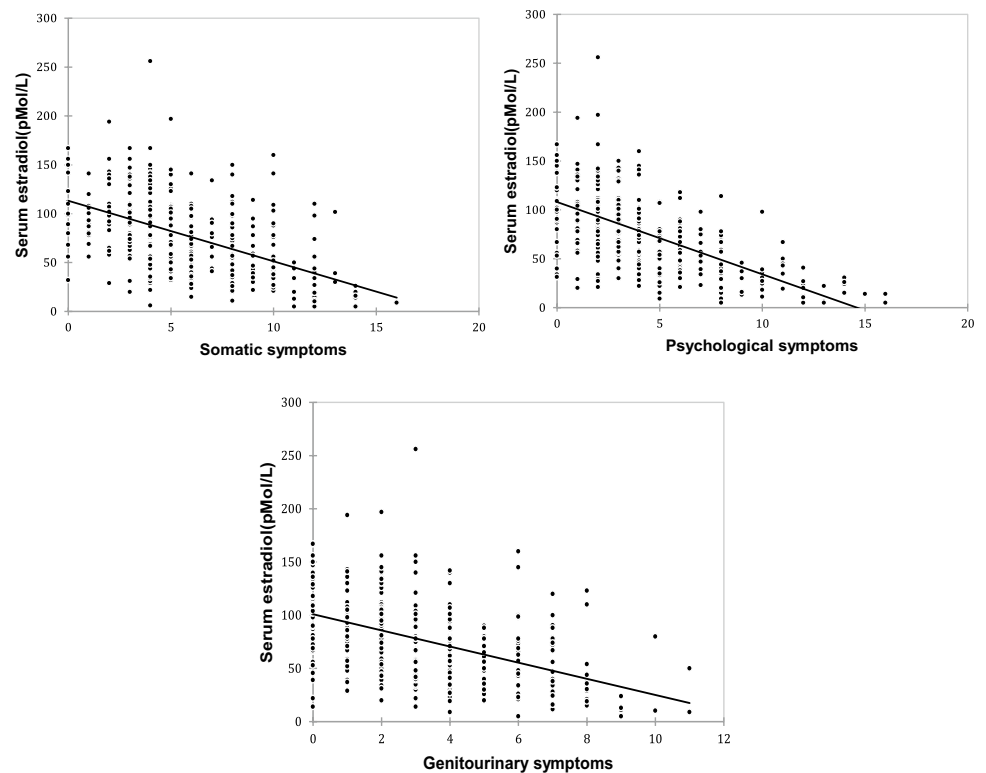
Fig. 3 Correlation of somatic, psychological and genitourinary symptoms with serum estradiol (pMol/L)

aromatase. Estradiol is also produced in a number of extragonadal organs, including brain, fat, adrenal gland, skin. Blood vessels and bone have also been discovered to synthesize estradiol as they express aromatase activity. There are three major forms of physiological estrogens in females: estrone (E1), 17β-estradiol (E2) and estriol (E3). E1 and E2 are the 2 major biologically active estrogens in humans. A third bioactive E3 is the pregnancy estrogen produced by placenta but plays no significant role in non-pregnant. E2 is the major product from the whole biosynthesis process and is the most potent estrogen during the premenopausal period in a woman's life, whereas E1 plays a larger role after menopause. E1 and E2 are mutually convertible, and E2 is 3–5 times more potent than E1. At menopause, the granulose cells become atretic and theca cells continue to synthesize androgens for some time which is converted to estrogens and extragonadal sites come into play. A major difference is that the tissues and cells of the extra-gonadal sites of estrogen synthesis are unable to synthesize C19 steroids but are able to convert circulating C19 steroids to estrogens

using aromatase. This extragonadal synthesized estrogen is thought to act locally which limits its systemic effects [2].

There are three major forms of physiological estrogens in females: estrone (E1), 17β-estradiol (E2) and estriol (E3). Estrogens act through 2 types of their receptors: classical nuclear receptors (ERα and ERβ) and novel cell surface membrane receptors (GPR30 and ER-X). Estrogen receptors have been found in brain and periphery including adipose tissue, bone, kidney, blood vessels and skin [2, 3].

In reproductive years serum E2 value is 30–400 pg/mL, but after menopause, it falls below 30 pg/mol or 141 pmol/L (vitros). For hormone measurement at relatively low circulating concentrations as in menopause, traditional immunoassays such as ELISAs (enzyme-linked immunosorbent assay) commercial E2 assay suffer from cross-reactions and low reproducibility [4].

In western world, menopause occurs at a mean age of 51–52 years [5]. Menopause is earlier in Indian women as compared to western countries by 4–5 years. We found mean age of menopause in our study population was found to be

47.2 ± 3.96 years ranging from 46 to 50 years. As per Indian menopausal society, the average age of menopause in Indian women is 47.5 years. Other Indian studies have also found mean age of menopause was 48.9 years [6]. The most common menopausal symptom reported in our study was joint pain (67.25%). Joint pain, hot flushes, sleep disturbance and physical and mental exhaustion were the severe symptoms experienced by our study group. This finding was consistent with other Indian studies [6, 7]. Joint pains and sarcopenia are more troublesome than hot flushes in Indian women interfering with their day-to-day activities. It is another hall mark of menopause [8]. In our study, sexual problems were reported by (42.25%). Other studies have reported similar incidence from 12 to 45% [9].

Serum estradiol in postmenopausal women is less than 141 pMol/L, according to our laboratory reference values. The mean serum estradiol of study population was 77.23 ± 39.35 pMol/L with median of 78 pMol/L. The range of serum estradiol was from 5 to 256 pMol/L.

We found incidence of hot flushes, and night sweats were found to be 53.5% in our study population. Hot flushes are more common and severe in western population, seen in 50–82% [9–11]. Asian studies have found similar lower incidence [6, 12]. In our study out of all 3 subscales of MRS, highest score rated, i.e., most severe symptoms were the somatic symptoms and then psychological symptoms followed by genito-urinary symptoms.

All the 11 questions pertaining to menopausal symptoms showed strong correlation with serum estradiol values. Hot flushes ($p < 0.002$), heart discomfort ($p < 0.001$), sleep disturbance ($p < 0.001$), depressive mood ($p < 0.001$), irritability ($p < 0.001$), anxiety ($p < 0.001$), physical and mental exhaustion ($p < 0.001$), sexual problems ($p < 0.003$), bladder problems ($p < 0.001$), dryness of vagina ($p < 0.001$) and joint and muscular pain ($p < 0.002$) showed strong correlation with declining serum estradiol values.

Among somatic symptoms, the mean value of serum estradiol was 73.28 pMol/L, 72.52 pMol/L, 67.41 pMol/L 58.07 pMol/L for muscle and joint pain, hot flushes, sleep disorders and heart discomfort, respectively. There was highly significant correlation seen with somatic symptoms and falling estradiol values (correlation coefficient of −0.532).

Psychological symptoms increase at menopause [13]. In Psychological subscale, the mean value of serum estradiol was 66.99 pmol/L, 64.66 pmol/L, 62.4 pMol/L, 61.62 pmol/L, in physical and mental exhaustion depressive mood, irritability and anxiety, respectively. There was highly significant correlation seen with psychological symptoms and falling estradiol values (correlation coefficient −0.619). Estrogen affects the mood-regulating pathways of the brain: Depression is thought, albeit in part, to be caused by dysregulation of the monoaminergic pathways in the central nervous system, and changing estrogen levels can lead to alterations of these serotonergic and noradrenergic systems [14]. Maximum inverse correlation of falling estradiol in our study was with psychological symptoms.

In genito-urinary subscale, the mean values of serum estradiol were 69.52 pmol/L, 66.29 pMol/L and 64.13 pMol/L in sexual problems, bladder problems and vaginal dryness, respectively. There was highly significant correlation seen with genito-urinary symptoms and falling estradiol values (correlation coefficient of −0.495).

The correlation between serum estradiol and total MRS score showed inverse correlation which was of high statistical significance (p value < 0.001).

We had 19 patients out of 400 (5.25%) showing higher serum estradiol values than the reference limit for menopause (141–256 pMol/L). Only 2 had a score of 0 with minimal symptoms. Only 2 were asymptomatic with score of 0 0.17 that had different postmenopausal symptoms. Three patients were less than 50 years, and 14 had BMI more than 23, which could explain higher estradiol in these patients. This is also reported by some researchers in a case report in which no identifiable cause could be found. It can be hypothesized that these patient underwent a cross-reaction with irregular antibodies. Serum estradiol values may be increased in ingestion of contaminated maize, granulosa cell tumor, cirrhosis liver or adrenal tumors where levels are very high [15]. These patients had normal examination and normal investigations. Apart from research activities serum estradiol is not recommended in diagnosis of postmenopausal symptoms or to see response of estrogen replacement where commonly symptomatic relief is considered.

Our study showed a strong correlation between the common postmenopausal symptoms and serum estradiol levels. A judicious hormonal replacement, research for newer estrogen analogues with greater safety margin and life style modification is needed to alleviate the suffering associated with menopause.

Conclusion

The menopausal symptoms in our population showed strong correlation with serum estradiol values. Inverse correlation with serum estradiol was seen with psychological, somatic and genito-urinary postmenopausal symptoms in descending order. In our study out of all 3 subscales of MRS, highest score rated, i.e., most severe symptoms were somatic symptoms and then psychological symptoms followed by genito-urinary symptoms.

Declarations

Conflict of interest The authors declare that they have no conflict of interest statement.

Ethical approval Ethical clearance for the study was taken from hospital ethics committee with number-TP(MD/MS)(98/2018)/IEC/ 1931 (attached as supplementary file).

Informed Consent Written informed consent of all study subjects was taken.

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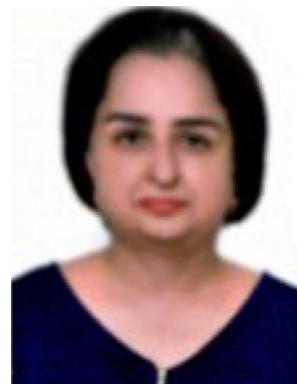
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