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Clinical and biochemical compare of perimenopausal and menopausal women

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Abstract: *Background:* Menopause is an integral part of female normal physiology as outcomes of most vital non-modifiable risk factor of aging with symptoms ranging from trivial to ominous. *Objectives:* To compare levels of Serum free T4 (fT4), Thyroxine (T4), Thyroid-Stimulating Hormone (TSH), Total Cholesterol, low-density lipoprotein-cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), Triglyceride, Total calcium, Total phosphorus, Serum alkaline phosphatase (ALP) and Vitamin D3. *Methods:* An open label analytical cross-sectional non-interventional study was conducted on 120 consecutive female patients in their perimenopausal and menopausal phases of life at the departments of Biochemistry and Obstetrics & Gynecology of the tertiary care teaching institute of eastern India from October 2023 to March 2024. *Results:* Thyroid, Calcium and Lipid profiles of 60 perimenopausal women were compared with that of 60 menopausal women. fT4, T4 and TSH levels were lower among menopausal group though not statistically significant. In menopausal group, mean Calcium levels were higher and phosphors levels lower than perimenopausal group without significant difference. Mean ALP levels in menopausal group were higher, while Mean Vitamin D3 levels lower; both disparities were highly significant. Mean Cholesterol and Triglyceride levels were significantly higher in menopausal group. Mean LDL-C levels were higher and Mean HDL-C was lower in menopausal women; these differences insignificant. *Conclusion:* Our study suggests a necessity to assess functional status and metabolic transition in Thyroid, Calcium and Lipid profile periodically in the perimenopausal and menopausal period to limit morbidity, disability and mortality risks.

Keywords: Menopause, Perimenopause, Calcium Profile, Lipid Profile, Thyroid Profile

Introduction

'Menopause' dates back to Greek words 'meno' (month) and 'paus' (to stop) means amenorrhea of consecutive 12 months after the age of 40 due to cessation of normal ovarian functions by 51 years of age [1]. These changes in ovarian functions lead to biochemical, physiological and clinical manifestations which are ill-understood [2]. SWAN study provided strong evidence on reproductive aging and changes of spectrum of lipid parameters while HDL-C has complex relationship in menopausal transition with the genesis of cardiovascular (CVD) risks [3-4].

The prevalence of metabolic syndrome and the clustering of its clinico-metabolic components increase the CVD risk during menopause outside the effects of chronological ages [5-6]. The variations in severity of the metabolic turmoil not only occur in menopausal women, but also its effects perimenopausal age spectrum [7-8]. Research group reported higher severity of metabolic disorders during perimenopausal period rather than post-menopausal period [9]. The research interest on hormone assay at menopause is rising due to evolving respect for women's health and related hormone replacement therapy [10-11].

There is scarce literature on calcium metabolism, dyslipidemia, and thyroid disorders amid outcome analysis of age range around the menopause from India and South-

East Asian countries. In the above scenario, the investigators of the present study attempted to explore clinical and physiological features among perimenopausal and menopausal women from rural Bengal to find interdependence of biochemical profile.

Material and Methods

This open label analytical cross-sectional non-interventional study was conducted on 120 consecutive female in their peri-menopausal (n=60) and menopausal (n=60) phases of life at the Departments of Biochemistry, and Obstetrics & Gynecology at the Midnapore Medical College and Hospital from October 2023 to March 2024 using pre-tested data collection tool. The tool was prepared with consultation from the subject experts at the Midnapore Medical College and Hospital with objectives to find levels of Serum free T4 (fT4), Thyroxine (T4), Thyroid-Stimulating Hormone (TSH), Total Cholesterol, low-density lipoprotein-cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), Triglyceride, Total calcium, Total phosphorus, Serum alkaline phosphatase and Vitamin D3.

Inclusion Criteria: Consecutive perimenopausal and menopausal women attending the out-patients departments without co-morbidities and not seriously ill were recruited.

Exclusion Criteria: Diabetes mellitus, thyroid etc. co-morbidities on interventions, licit & illicit drug users, pregnancy, on menopausal hormone therapy and hormonal contraceptive users.

Primary Outcome Variables: fT4, T4, TSH, Total Cholesterol, LDL-C, HDL-C, Triglyceride, Total calcium, Total phosphorus, Serum alkaline phosphatase and Vitamin D3 levels.

Data Collection Procedure: Our research data collection was initiated after approval from Institute Ethics Committee. Informed consent process was done with best possible sincerity. Each participant was individually counseled regarding the study objectives and ensured that the data will only be used for research purpose and will not hamper the course of treatment irrespective of their participation or if they leave the study in the midway for any reason. Written informed consent was obtained from each participant without coercion in vernacular and were asked to complete the menopause rating scale. A detailed history taking followed clinical assessment including vital parameters, anthropometry and systematic examinations for clinico-physiological changes of menopause with relevant investigations. The Principal investigator and the Co-investigators ensured privacy during interview and examination for collection and documentation of data. Ethical principles were adhered during data gathering with strict confidentiality and Helsinki declaration was followed in letter and spirit including data sanctity.

Data Analysis: Data were cleaned, collated and analyzed using Microsoft Excel (Microsoft Corp, Redmond, USA) and IBM SPSS Version 21.0 (IBM Corp, Armonk, USA); descriptive statistics and Z Test was used to find the statistical correlation between the categorical variables with alpha level of five percent accepted as significant.

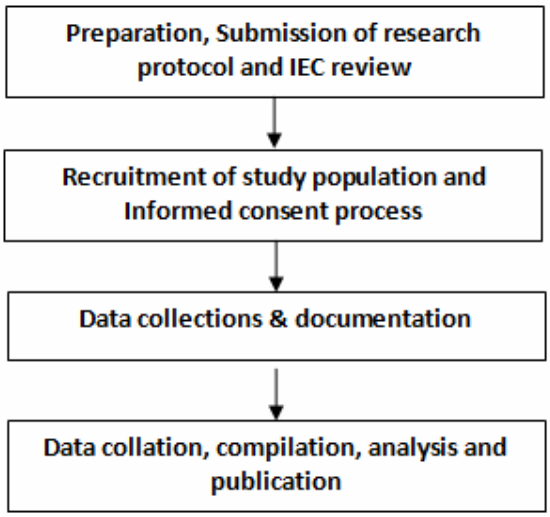
Operational Technical Information and Parameters: Perimenopause and menopause were defined as per recommendations from the global and Indian experts [12-13]. Unhemolysed blood samples (10ml) were aseptically collected after 12 hours fasting with universal precautions in single needle prick critically abiding biomedical waste management rule from antecubital vein; sample was allowed to clot in aliquot at room temperature for 2 hours and centrifuged at 3000 rpm for 10 minutes to separate the serum.

Thyroid Profile: Serum free T4 (fT4), T4, TSH was estimated using Electro-Chemi-Luminescence (eCLIA) assay [14]. LIPID PROFILE: Total cholesterol (TC) was quantitatively assessed by CHOD-PAP technique as per Allian [15]. Triglyceride was quantitatively assessed by GPO-ESPAS technique as per Bucolo and David [16]. HDL was quantitatively assessed by PEG-PAP method [17]. LDL level was estimated using Friedewald formula [18-19] from other lipid parameters in Cobas Integra 400 plus [20].

Calcium Profile: Serum Calcium and Phosphate: Bapta method in Cobas Integra

400 plus [20]; Alkaline phosphatase by IFFC method in Cobas Integra 400 plus [20]. Vitamin D3: eCLIA assay method in Roche Cobas e411 [14, 21].

Flow diagram of the study was as follows:



Results

This study explored three biochemical profiles amid clinic-physiologic processes among 120 consecutive female patients related in two groups of perimenopausal (n=60) and menopausal (n=60) phases of life. Serum free T4 (fT4), Thyroxine (T4), Thyroid-Stimulating Hormone (TSH), Total Cholesterol, low-density lipoprotein-cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), Triglyceride, Total calcium, Total phosphorus, Serum alkaline phosphatase (ALP) and Vitamin D3 levels were assessed. An effort to find their interdependence of clinico-physiological states of peri-menopause and menopause was explored. Mean ages of perimenopausal and menopausal women were 44.16±3.57 and 53.63±4.85 years respectively.

THYROID PROFILE:

Free T4 (fT4): In our study fT4 levels among perimenopausal women were 1.66±0.19 and 1.31±0.19 ng/dL in menopause group. However, this difference was not significant (p=0.536998).

Thyroxine (T4): Mean T4 levels among perimenopausal women was 8.41±0.53in contrast to 7.65± 0.34 µg/dL in menopause. However, this difference was also not significant (p=0.579727).

Thyroid-Stimulating Hormone (TSH): Mean TSH of perimenopausal and menopausal women were 4.31±0.92 and 3.46±0.90µIU/L respectively. However, this difference was also not significant (p=0.588457) [Table 1].

Table-1: Thyroid profile of Perimenopausal and Menopausal women (n=120)

Parameters	Perimenopausal women (n=60) Mean ± SD	Menopausal Women (n=60) Mean± SD	z-value	p-value	Remarks significance level at p<0.05
fT4 (ng/dL)	1.66±0.19	1.31±0.19	0.098723	0.536998	Not significant
T4 (µg/dL)	8.41±0.53	7.65± 0.34	0.201194	0.579727	Not significant
TSH (µIU/L)	4.31±0.92	3.46±0.90	0.223578	0.588457	Not significant

ng/dL = nanograms per deciliter, µg/dL=micrograms per deciliter, µIU/L= micro-international unit per liter,

CALCIUM PROFILE:

Total Calcium: In our study Mean Calcium levels among perimenopausal women was 7.8±0.80 and 9.32±0.69 mg/dL in menopause. However, this difference was not significant (p=0.344475).

Total Phosphorus: Mean Serum total Phosphorus levels among perimenopausal women was 4.8±0.50 and 4.01± 0.63 mg/dL in menopause; this difference was insignificant (p=0.582299).

Serum alkaline phosphatase (ALP): Mean ALP levels in perimenopausal and menopausal women were 175.77±26.66 and 278±25.80 IU/L respectively; disparity was statistically highly significant (p=0.0000001).

Vitamin D3: Mean D3 levels in perimenopausal and menopausal women were 63.05±7.90 and 51±7.10 nmol/l respectively; the difference was highly significant (p=0.0007536) [Table 2].

Table-2: Calcium profile of Perimenopausal and Menopausal women (n=120)					
Parameters	**Perimenopausal women (n=60) Mean ± SD**	**Menopausal Women (n=60) Mean± SD**	**z-value**	**p-value**	**Remarks significance level at p<0.05**
Calcium (mg/dL)	7.8±0.80	9.32±0.69	0.400282	0.344475	Not significant
Phosphorus (mg/dL)	4.8±0.50	4.01± 0.63	0.207778	0.582299	Not significant
Alkaline phosphatase (IU/L)	175.77± 26.66	278± 25.80	26.9215	0.0000001	Highly significant
Vitamin D3 (nmol/L)	63.05± 7.90	51±7.10	3.173285	0.0007536	Highly significant
Units used in above table: mg/dL=miligrams per deciliter, IU/L= international unit per liter, nmol/L= nanomol per liter					

LIPID PROFILE:

Total Cholesterol: Mean Cholesterol levels in perimenopausal and menopausal women groups were 318.6 ± 22.35 and 333 ± 37.00 mg/dL respectively; this difference was statistically highly significant (p=0.0002856).

Low-density lipoprotein-cholesterol (LDL-C): Mean LDL-C levels in perimenopausal and menopausal women groups were 210.11 ± 19.15 and 213.1 ± 19.57 mg/dL respectively; this difference was statistically insignificant (p=0.215548).

High-density lipoprotein cholesterol (HDL-C): Mean HDL-C levels in perimenopausal and menopausal women groups were 37.48± 5.68 and 34.32± 6.05 mg/dL respectively; this difference was statistically insignificant (p=0.797342).

Triglyceride: Mean Triglyceride levels in perimenopausal and menopausal women groups were 318±15.80 and 331± 28.42 mg/dL respectively; this difference was statistically highly significant (p=0.0003091) [Table 3].

Table-3: Lipid profiles of Perimenopausal and Menopausal women (n=120)					
Parameters	**Perimenopausal women (n=60) Mean ± SD**	**Menopausal Women (n=60) Mean± SD**	**z-value**	**p-value**	**Remarks significance level at p<0.05**
Total Cholesterol (mg/dL)	318.6± 22.35	333± 37.00	3.792141	0.0002856	Highly significant
LDL Cholesterol (mg/dL)	210.11±19.15	213.1±19.57	0.7876	0.215548	Not significant
HDLCholesterol (mg/dL)	37.48± 5.68	34.32± 6.05	0.8321	0.797342	Not significant
Triglyceride (mg/dL)	318±15.80	331± 28.42	3.4234	0.0003091	Highly significant
Units used in above table: mg/dL=miligrams per deciliter					

Discussion

Menarche and menopause are integral part of normal physiology of healthy life of typical women, yet these extremes of their reproductive lives shows wide levels of inconsistency. Global review on menarche showed relative consistency of mean menarcheal age range of 12-13 years as secular trend, while in Indian populations varied from 15.2 to 12.5 years [22]. Research groups noted wide disparity of the age and uncertainty of the spectrum clinical features of natural menopause. In India menopause was reported mostly between 45-55 years as natural ageing process in absence of outcome of surgical or medical interventions. Perimenopause refers to long undefined time periods from first observed sign to end of one year after final menstrual period which may last several years affecting physical, emotional, mental and social well-being for which hormonal and non-hormonal interventions needed to alleviate clinical outcomes [8].

Menopause represents permanent cessation of menstrual periods and the loss of fertility - occur spontaneously (natural menopause) or surgically induced by bilateral oophorectomy. The symptoms and menopause-related complications are caused by decreased estrogen levels due to the loss of ovarian function. Menopausal symptoms vary widely as well as qualitatively depending on subjective and individualized threshold levels of tolerance levels: hot flushes and night sweats, psychological changes (viz. depression, and impaired concentration), insomnia, vaginal dryness, skin changes (viz. thinning and decreased elasticity) [23-24].

Clinical and biochemical changes at perimenopause and menopausal phases of lives have been attributed to estrogen and or progesterone depletion. Estrogens are considered important in maintenance of lipid and glucose homeostasis, and promote synthesis of proteins that maintain peripheral energy homeostasis. Progesterone regulates functions of the uterus, ovary, mammary glands and brain. Although the menopause is entirely natural, in some cases ovarian failure can occur earlier than usual that warrants across clinical disorders viz. endocrine, cardiovascular, skeletal, body mass, and sleep pattern. All these clinico-social issues are faced by health care workers need capacity building and supportive infrastructure along with standardized reference for screening and diagnostic tests around menopause. All these concerted activities need to be employed to interpret and intervene in clinical management of menopausal crisis as the hidden agenda of women empowerment [25].

Thyroid Profile: Hypothyroidism is most commonly occurring endocrinopathies, especially in subclinical cases; affects females 7-10 times more frequently, and manifests more during menopause. [26]. In our study mean Free T4 levels among perimenopausal women were 1.66±0.19 and 1.31±0.19 ng/dL among menopausal. However, this difference was not significant. University of California San Francisco declares typical normal range is 0.8-1.9 ng/dL [27]. In national level Korean study among disease-free population without known thyroid disease, family history of thyroid dysfunction, or current pregnancy, fT4 among 50 years and above females had mean of 1.18-1.20 and median of 1.16-1.19 ng/dL [28]. In our study mean T4 levels among menopausal women was lower than perimenopause (7.65± 0.34 µg/dL) without any significant statistical difference. This data closely resembled observation by other Indian research group (7.88±1.26 µg/dL) [29]. Similarly, mean TSH level at our study was 3.46±0.90 µIU/L in menopausal women matched Indian study mean TSH level of 3.39±2.45 µIU/mL at menopause [30].

Calcium Profile: In our study menopausal women had higher mean Calcium level and lower mean phosphors levels than women in their perimenopausal group which resembles findings of other Indian research group [31]. In our study Mean Vitamin D3 levels were lower at menopause than perimenopausal group that was statistically highly significant. Barring few exceptions, evidence of clinically important association as well as causation was established between D3 levels and menopause-related symptoms. Researchers from north-India noted decreased levels of serum vitamin D3 & serum calcium and increased level of serum phosphorus in postmenopausal women [31]. In our study Mean ALP level was significantly higher in menopausal women than perimenopausal women. Research groups have long back noted that rise in plasma alkaline phosphatase may reflect the onset of bone loss at menopause [32-33].

Lipid Profile: Mean Cholesterol and Triglyceride levels both were significantly higher in menopausal women than perimenopausal women in our study; mean LDL-C and HDL-C levels both were also elevated in menopausal women group though not statistically significant. Estrogen affects lipoprotein metabolism on LDL-lipoprotein by increasing catabolic rate and hepatic receptors of LDL, and on HDL-lipoprotein by increasing HDL-lipoprotein synthesis, decreased HDL clearance and reduced hepatic receptors of HDL. Thus in menopause reverse effects occurs in gradual estrogen deficiency on lipid profile by increasing total cholesterol, low density lipoproteins and triglycerides as well as by decreasing High density lipoprotein. All these in downstream effect augments atherogenic pathogenesis with

streamlined proportional cardiovascular morbidity with age-matched male counterparts in women with natural menopause without hormone-replacement therapy by decline of serum levels of HDL cholesterol, and increase in levels of low-density lipoprotein cholesterol. However, in menopausal women with hormone-replacement therapy, it is noted that HDL and LDL cholesterol levels usually remain comparable with their perimenopausal counterparts, yet the levels of triglycerides remain at greater than before menopause [3]. Research group from South-Indian study concluded that hormonal paradigm of the menopause leads to changes in lipid profile by reducing HDL, and elevating total cholesterol, triglycerides, LDL-cholesterol, thus increasing the risk for cardiovascular disease at post-menopausal phases of lives [34].

Strengths of the study: This novel study was conducted on the major metabolic transition at menopausal phases of women viz. Thyroid, Lipid and Calcium profiles were compared among the participants in perimenopausal and menopausal groups to find baseline data for eastern India.

Limitations of the study: We had several limitations. Firstly, this study, being a cross-sectional study, was not able to unearth the depth of grass-root level risk factors and outcome issues amid menopause. Secondly, this was a single centre study in peripheral medical college with hinterland of mainly rural population. Lastly, as a self-funded study the sample size was small and could not be extended to all the variables related to menopausal transition.

Future directions of the study: Our research group is yet to find big lot of Indian literature on conceptual, contextual, and translational aspects of Biochemical profiles of menopause. Our future studies will holistically focus on the clinic-physiological aspects of menopause from comparable globally published literatures to find feasibilities as well as applicability in our set up of research following Good Clinical Practice.

Conclusion

In our study, a higher tendency of subclinical hypothyroidism, dyslipidemia and disorders of Calcium metabolism in menopausal women was observed. This suggests dire necessity to initiate standard office procedure by the clinical practice guideline assess subtle changes of women above 40 years of age. Screening of functional status and metabolic transition in these basic biochemical profiles periodically in post-menopausal period can limit morbidity, disability and mortality risks. We find suitability of user-friendly and cost-effective common biomarkers for prognosis of menopausal transition that contributes to alleviate these risks.

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