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A Study of Hematological Biomarkers in Depressed Postmenopausal Females

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Abstract

Context: Due to the heterogeneity in the occurrence of depression in postmenopausal women and a lack of adequate data on correlation of severity of depression with the co-occurrence of thyroid, lipid and vitamin metabolism derangements in these women, this study was planned to examine the prevalence of these derangements and its correlation with severity of depression in depressed postmenopausal women.

Aims: The aim of the study was to find out the prevalence and correlation of TSH, Lipid Profile, Folate and Vitamin B12 derangements with the severity of depression in postmenopausal women.

Settings and design: A cross-sectional study was carried out at the Department of Psychiatry and Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur. After screening 150 consecutive depressed postmenopausal females (age group of 45-60 years), 40 females and 40 healthy female controls, matched socio-demographic profile were included in the study.

Materials and methods: After taking written informed consent, all subjects were assessed using Hamilton rating scale for depression, Menopausal rating scale and blood levels of TSH, lipid profile, folate and vitamin B12 was assessed.

Statistical analysis used: Group comparisons were done with chi-square test, T-test and Pearson's correlation, with help of SPSS, ver. 21.0.

Results: There is significantly more prevalence and correlation of TSH and lipid profile derangements in depressed post-menopausal women, and the derangement in TSH levels worsens with the severity of depression. The folate levels are also significantly worse in the depressed group, but not Vitamin B12. Both did not correlate with severity of depression in the current study.

Conclusion: Management of thyroid and lipid derangements can help manage depression in post-menopausal women more holistically. The role of folate and vitamin B12 replenishment can also be considered when judging treatment response in these patients.

Keywords: Depressed; Postmenopausal women; Blood biomarkers; TSH; Lipid Profile; Folate; Vitamin B12

Introduction

Depression is a common and costly disorder [1] which is usually associated with severe and persistent symptoms leading to important social role impairment and increased mortality [2]. It is one of the most important causes of disability worldwide [3]. Epidemiological studies worldwide report the prevalence of major depressive disorder about twice as high in women compared to those in men, especially during the childbearing years and may increase during menopause [4,5]. Depression may be debilitating, decreases quality of life and many patients may not respond to antidepressant treatment or may discontinue drug therapy due to side effects [6]. Neurobiological studies demonstrate that Estrogen regulates numerous aspects of Noradrenergic, Serotonergic, GABAergic and Dopaminergic transmission and may substantiate mood and depressive states [7].

Relationship between menopause and depression has not been clearly defined. However, clinical studies report altered mood and reduced libido in women during menopause [8,9]. It is reported that women are most likely to develop mood symptoms (i.e., depressed mood, apathy) during the mid to late-luteal phase of their menstrual cycle, a period during which Progesterone levels are peaking while Estrogen levels are declining [10]. Many of these women who experience physical and neuropsychiatric symptoms of menopause have a diminished quality of life [11] and decreased functionality [12].

There is increased occurrence of thyroid dysfunction in menopausal women and may affect 10–15% of postmenopausal women [13]. A study [14] suggested that natural menopause affects lipid metabolism adversely, particularly Plasma lipoproteins and cholesterol levels [15]. Total Cholesterol, LDL (Low density Lipoproteins) levels and Triglyceride levels are increased, while, the HDL (High density Lipoproteins) levels are decreased in postmenopausal women, more than premenopausal women of same age and BMI (Body Mass Index) [16]. Recent epidemiological and clinical studies investigating the relationship between serum cholesterol levels and depressive symptoms have yielded equivocal results [17,18]. It has been reported that disturbances in folate-dependent one-carbon metabolism may contribute to neurodegenerative diseases, including depression [19]. Folate, a naturally occurring B vitamin, is necessary for the synthesis of the trimonoamine neurotransmitters implicated in depression and may

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enhance the effects of a traditional antidepressant [20]. The Rotterdam study of older men and women found that hyperhomocysteinemia, vitamin B12 deficiency and folate deficiency were related to depressive disorders [20]. Another study also suggested an inverse relationship between serum folate and depressive symptoms [21]. An improved response to antidepressants is reported in postmenopausal women when administered in combination with folic acid and vitamin B supplements; thus, folate and vitamin B status might be related to depression [21].

Due to the heterogeneity in the occurrence of depression in postmenopausal women and a lack of adequate data on correlation of severity of depression with the co-occurrence of thyroid, lipid, folate and vitamin B12 derangements in these women, this study was planned to examine the prevalence of thyroid, lipid, folate and vitamin B12 level derangements and its correlation with severity of depression in depressed postmenopausal women.

Aim

The aim of the study was to find out the prevalence and correlation of TSH (Thyroid Stimulating Hormone), Lipid, folate and vitamin B12 derangements with the severity of depression in postmenopausal women.

Methodology

A cross-sectional study was carried out at the Department of Psychiatry and Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur. After screening 150 consecutive depressed postmenopausal females (age group of 45-60 years) [10], 40 females were included in the study as per the inclusion and exclusion criteria that were set. An equal number of controls were recruited which were matched to the cases on sociodemographic profile.

Inclusion criteria for cases (depressed postmenopausal females)

1. Females who met the ICD-10 criteria for Major depression, diagnosis being confirmed by a senior psychiatrist.
2. Those who were in the age group of post-menopause, i.e., 45-60 years.
3. Those whose menopause had set in >/=12 months back [22].
4. Those who were drug naive, both psychiatric and hormonal drugs included.
5. Those who could understand the nature of the study and willing to give informed consent for participation.

Exclusion criteria for cases

1. Those who could not communicate well, either by virtue of intellectual impairment or any physical impairment.
2. Those with significant physical or neurological illness.
3. Any evidence of co-morbid psychiatric disorder other than depression.
4. Those having a prior history of psychiatric illness or of having received any hormonal or psychiatric treatment.
5. Those who were not willing to give informed consent.

Inclusion criteria for controls (non-depressed postmenopausal females)

1. Those who were in the age group of post-menopause, i.e., 45-60 years.
2. Those whose menopause had set in >/=12 months back [22].
3. Those who were drug naive, both psychiatric and hormonal drugs included.
4. Those who could understand the nature of the study and willing to give informed consent for participation.
5. Those who scored <7 on Hamilton rating scale for depression (<7=No depression)

Exclusion criteria for controls

1. Those who could not communicate well, either by virtue of intellectual impairment or any physical impairment.
2. Those with significant psychiatric, physical or neurological illness.
3. Those having a prior history of psychiatric illness or of having received any hormonal or psychiatric treatment.
4. Those who were not willing to give informed consent.

Tools of Study

1. Sociodemographic form: This was a semi-structured investigator filled form which contained the details of sociodemographic profile of the patient. The socioeconomic status was recorded as per the modified Kuppuswami Index [23].
2. Hamilton's Rating Scale for Depression (HAM-D) [24]: It is the most widely used clinician administered depression assessment scale. It contains 17 items pertaining to symptoms of depression experienced over the past week and is used to assess the severity of depressive symptoms. It takes 20-30 minutes to administer. A score < or = 7 is considered normal, 7-13 (mild depression), 14-24 (moderate to severe depression), >24 (severe depression).
3. Menopause rating scale [25]: It is a 11-item clinician administered scale to assess the various menopausal symptoms and assess its severity on a likert scale from 0 (no symptoms) to 4 (very severe symptoms). It takes about 10 min to administer. In this study, we have used it as a reference for listing presence or absence of menopausal symptoms only, as assessment of severity was not in the scope of this study.
4. Blood investigations: Blood samples of all subjects were collected for testing TSH, lipid, folate and vitamin B12 levels in the morning after an overnight fasting of 10-12 h. 5 ml of venous blood was drawn and assessed in laboratory. Serum lipid profile and TSH were assessed using the auto-analyser (Selectre-E and Micro lab-300) and Automated- immunoassay analyser (Immulite 1000) by using commercially available reagents and kits. Serum folate and serum vitamin B12 levels were assessed on automated machines by Chemiluminicent Immunoassay (C.L.I.A).

Statistical Analysis

Descriptive data was analysed in frequencies, mean and standard

deviations. Comparison and correlations among groups was established using chi-square tests, independent T-tests and Pearson's correlation. The results were considered significant at $p<0.05$. All tests were applied using the software, SPSS, ver. 21, IBM Corp.

Results

The depressed and non-depressed postmenopausal females groups did not differ significantly from each other in the sociodemographic profile. Most of the females belonged to Hindu religion (30 and 33, respectively) and lower socioeconomic status (30 and 28, respectively). Nuclear family was the predominant family type (27 and 22, respectively) and majority of females were housewives (30 and 35, respectively) (Table 1).

The depressed and non-depressed postmenopausal female groups differed significantly from each other on parameters of heart discomfort (p=0.023), physical and mental exhaustion (p=0.010), sexual dysfunction (p=0.045), bladder dysfunction (p=0.050), depressive mood (p=0.000), irritability (p=0.000), anxiety (p=0.000) and joint and muscle aches (p=0.000) (Table 2).

The depressed and non-depressed postmenopausal female groups differed significantly in serum levels of cholesterol (p=0.023), triglycerides (p=0.020) and HDL (p=0.000), TSH (p=0.042), Folate (p=0.036), Vit B12 (p=0.002). There was no significant difference in levels of LDL and VLDL (Table 3).

The depressed and non-depressed postmenopausal females differed significantly in serum levels of TSH and folate. There was no difference in vitamin B12 levels (Table 4).

The HAM-D scores of depressed postmenopausal females correlated significantly with serum levels of TSH (p=0.000), cholesterol (p=0.000), triglycerides (p=0.000), HDL (p=0.000) and LDL levels (p=0.000) (Table 5).

Sociodemographic profile		Groups		X^{2*} (d.f.)	Signi † (2-tailed)
		Depressed pm females	Non-Depressed Pm Females		
Age group	<=48 years	15	15	0.720 (2)	0.698
	49-52 years	11	14		
	53+ years	14	11		
Religion	Hindu	30	33	0.672 (1)	0.412
	Muslim	10	7		
Socioeconomic status	Lower	30	28	1.736 (2)	0.420
	Middle	6	10		
	Upper	4	2		
Family type	Nuclear	27	22	1.317 (1)	0.251
	Joint	13	18		
Occupation	Housewife	30	35	2.051 (1)	0.152
	Service	10	5		

*Chi Square test value, †Significance

Table 1: Sociodemographic profile.

Menopausal rating scale parameters		Group		X^{2*} (d.f.)	Signi† (2-tailed)
		Depressed pm females	Non-depressed pm females		
Hot flushes	Absent	10	16	2.051 (1)	0.152
	Present	30	24		
Heart discomfort	Absent	2	9	5.165 (1)	0.023
	Present	38	31		
Sleep disturbances	Absent	7	11	1.147 (1)	0.284
	Present	33	29		
Physical and mental exhaustion	Absent	3	12	6.646 (1)	0.010
	Present	37	28		
Sexual dysfunction	Absent	4	11	4.021 (1)	0.045
	Present	36	29		
Bladder dysfunction	Absent	8	16	3.810 (1)	0.050
	Present	32	24		
Dryness of genital tract	Absent	6	11	1.867 (1)	0.172
	Present	34	29		
Depressive mood	Absent	9	27	16.364 (1)	**0.000**
	Present	31	13		
Irritability	Absent	8	27	18.337 (1)	**0.000**
	Present	32	13		
Anxiety	Absent	7	25	16.875 (1)	**0.000**
	Present	33	15		
Joint and muscle aches	Absent	6	21	12.579 (1)	**0.000**
	Present	34	19		

*Chi Square test value, †Significance

Table 2: Menopausal rating scale.

Lipid Profile Parameters (mg/ml)	Group	Mean (s.d.)	t-Value* (d.f.)	Signi† (2-tailed)
Cholesterol	Depressed PM Females	160.08 (18.868)	2.314 (78)	0.023
	Non-Depressed PM Females	151.43 (14.241)		
Triglycerides	Depressed PM Females	92.83 (24.516)	2.368 (78)	0.020
	Non-Depressed PM Females	80.83 (20.651)		
HDL	Depressed PM Females	44.40 (5.647)	-4.622 (78)	0.000
	Non-Depressed PM Females	51.25 (7.482)		
LDL	Depressed PM Females	98.55 (19.155)	1.795 (78)	0.077
	Non-Depressed PM Females	92.38 (10.317)		
VLDL	Depressed PM Females	19.13 (3.653)	1.524 (78)	0.132
	Non-Depressed PM Females	17.90 (3.536)		
TSH	Depressed PM Females	6.23 (2.49)	1.013 (78)	0.036
	Non-Depressed PM Females	3.74 (1.03)		
Folate	Depressed PM Females	5.110 (1.73)	1.626 (78)	0.042
	Non-Depressed PM Females	6.634 (2.11)		
Vit B12	Depressed PM Females	150.40 (41.19)	3.034 (78)	0.002
	Non-Depressed PM Females	176.35 (59.60)		

*Independent t-test value, †Significance

Table 3: Blood biomarkers mean values.

Serum levels		Group		X^{2*} (d.f.)	Signi† (2-tailed)
		Depressed pm females	Non-depressed pm females		
TSH (mcg/mL)	<4.00	22	31	4.528 (1)	0.033
	>4.00	18	9		
Folate (ng/mL)	<=5.5	18	8	5.698 (1)	0.017
	5.5+	22	32		
Vitamin B12 (pg/mL)	<=211	37	36	0.157 (1)	0.692
	212+	3	4		

*Chi square test value, †Significance

Table 4: TSH, B12, Folate levels.

Correlations		TSH	Cholesterol	Triglycerides	HDL	LDL	VLDL	Vitamin b12	Folate
HAM-D	**Pearson's Coefficient**	0.672	0.886	0.913	-0.565	0.872	-0.208	0.083	-0.061
	Asymptotic Significance	0.000	0.000	0.000	0.000	0.000	0.197	0.609	0.708

Table 5: Correlations.

Discussion

Women in the menopausal transition and the postmenopausal period are affected with vasomotor symptoms, urogenital atrophy, sexual dysfunction, somatic symptoms, cognitive difficulty, sleep disturbance and psychological problems [15]. The psychological symptoms such as depression, loneliness and despair tend to persist longer than physiological symptoms [26-29]. 19% post-menopausal women in the community report depressive symptoms and around the same number report thyroid and lipid profile derangements [15]. It has been suggested that folate and vitamin B12 have a role in depression, but the results of epidemiologic studies on this issue have been inconsistent. It is hypothesized that the deficiencies in folate and vitamin B12 can lead to elevated homocysteine concentrations, which have been associated with depression [30-33]. Hence we decided to study the prevalence and correlation of these factors in this study.

The depressed postmenopausal females group had significantly higher climecteric symptomatology than the non-depressed group, particularly on parameters of heart discomfort, physical and mental exhaustion, sexual dysfunction, bladder dysfunction, depressive mood, irritability, anxiety and joint and muscle aches. No differences were found in prevalence of hot flushes, sleep disturbances and dryness of genital tract. These symptoms are more attributed to estrogen and progesterone level fluctuations [34], rather than the thyroid, lipid and vitamin derangements that this study focused on.

The depressed and non-depressed postmenopausal female groups differed significantly in serum levels of TSH, cholesterol, triglycerides and HDL. There was no significant difference in levels of LDL and VLDL. The HAM-D scores of depressed postmenopausal females correlated significantly, positively with serum levels of TSH, cholesterol, triglycerides, LDL and negatively with HDL levels. This meant that depressed group had greater derangement in the TSH levels and lipid profile than the non-depressed group. Also, as the severity of depression increased, the serum levels of TSH, cholesterol, triglycerides and LDL increased, while those of HDL decreased. Another study also found similar results [35] but there is also a study [34] that had findings contrary to our study, where they didnot find significant correlation between severity of depression and deranged lipid profile. Even mild thyroid failure, as seen by raised TSH levels, can have a number of

clinical effects such as depression, memory loss, cognitive impairment and a variety of neuromuscular complaints in post-menopausal women [36] and hence the need to study its contributory role in postmenopausal depression. There are studies that report TSH derangements of the same tune as our study [16].

The depressed and non-depressed postmenopausal females differed significantly in serum levels of folate but there was no difference in vitamin B12 levels. Neither level correlated with severity of depression in postmenopausal females. Likewise, other studies [32,37] also found no statistically significant relationship between depressive symptoms and either folate or vitamin B12 level in postmenopausal women in our study. Although theoretically, the consumption of folate and vitamin B complexes, through diet or supplementation, decreases the total plasma concentration of homocysteine and may enhance responses to standard antidepressant treatment. Treatment with vitamin B complexes can reduce the long-term prevalence of depression in at-risk people, such as stroke survivors [37].

Conclusion

In this study, the aim was to study the occurrence and correlation of thyroid, lipid, folate and vitamin B12 derangements in depressed and non-depressed postmenopausal females. This was intended to give an insight into the hematological parameters that could serve as biomarkers for depressed state in post-menopausal women. While we did have significant derangements of TSH, lipids and folate levels, vitamin B12 did not differ much. This could be attributed to the fact that non-vegetarian diets and consumption of over-the-counter multivitamins could have confounded these findings in our study population. Nevertheless, the correlation of depression severity and derangement of these hematological parameters (TSH, cholesterol, triglycerides, LDL and HDL) were established. Though, we did not find significant correlation between severity of depression and levels of folate and vitamin B12, it would still be interesting to see the effect of replenishment of these vitamins and their effect on depression and its response to treatment, as suggested by multiple theoretical studies. The management of these non-psychiatric causes of morbidity will enhance the achievement of healthy life for patients of postmenopausal depression. The small sample size and cross-sectional study design have limited our study from being generalized but it definitely serves as a stimulus for future studies which can give us large evidence base in the field of management of postmenopausal depression.

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