

Comorbidity of recurrent depressive disorder with thyroid dysfunction and altered lipid metabolism in postmenopausal women: A case-control study

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Abstract

The transition to menopause represents the passage from reproductive to non-reproductive life. Most women during the menopause experience irregular menstrual periods along with fluctuation of ovarian hormones secretion during this time. Usually during the menopause and after menopause i.e. post-menopause women face physical and emotional changes. Since years various investigators have already documented an association between depression and menopause. Post-menopausal period is accompanied in a majority of women with significant somatic and psychiatric symptomatology. **Objective:** Since psychiatric symptomatology is a growing concern in post-menopausal women, hence we tried to examine whether a comorbidity of metabolic and psychiatric disorders occurs in this patient population or whether these disorders occur independently. The study was planned to examine comorbidity of recurrent depressive disorder with thyroid dysfunction and altered lipid metabolism in post-menopausal women (PMW). **Method:** To conduct this study a cross sectional, case-control study was planned. The experimental group consisted of PMW with recurrent depressive disorder (ICD-10 criteria) (n=100), and was compared with a control group (n=100) of PMW without recurrent depressive disorder. Subjects were assessed through Beck's depressive self-rating inventory and their blood level of Thyroid Stimulating Hormone (TSH) and lipid profile was assessed. Group comparison was done with chi square test and z test. Correlation analysis was undertaken using Pearson correlation coefficients (r). **Result:** Results obtained depicted that serum total cholesterol, triglyceride, TSH levels were significantly higher and HDL levels were significantly lower in the depressed group. Highly significant positive correlation was found between Beck's score and TSH levels in depressed PMW. **Conclusion:** Taken together, these data demonstrated that comorbidity of recurrent depressive disorder with thyroid dysfunction and lipid metabolism abnormality in post-menopausal women is common and needs clinical attention.

Keywords: Depression, post-menopausal women (PMW), Thyroid dysfunction, lipid profile, Beck's depressive self-rating inventory.

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INTRODUCTION

Menopause is defined as the permanent cessation of ovulation and it represents the passage from reproductive to non-reproductive life. It generally occurs between 45-53 years of age. The marked fluctuations in reproductive hormones associated with this stage can lead to hot flashes, sleep disturbances, vaginal atrophy and dryness and cognitive and affective disturbances²⁶. More than 1 million women are expected to reach menopause each year, a majority of whom experience physical and neuropsychiatry symptoms that may diminish their quality of life whereas an estimated 20% have depression

at some point during menopause⁵⁶. Fifty percent of middle aged women experience a dramatic change in their emotion as well as change in physical states because of alteration in their hormone levels⁹. The psychological symptoms such as depression, loneliness and despair usually persist even after cessation of hot flashes, fainting, headache, palpitation and insomnia³². It is well documented that recurrent depressive disorder occurs about 2 times more frequently in women than in men³⁰ and may increase during time of menopause³. Studies have also shown that recurrent depressive disorder increases mortality and morbidity¹. There is an increasing incidence of subclinical and overt thyroid dysfunction in postmenopausal women. These conditions can be associated with climacteric symptoms, cognitive impairment and subtle neuromuscular abnormalities. Several investigations have shown that there is also an increase of LDL cholesterol and an increased risk for the development of arteriosclerosis and myocardial infarction⁴⁸. In 1989 Karen suggested that natural menopause affects lipid metabolism unfavourably²⁹. Menopause, with its well-known hormonal profile, is associated with adverse metabolic changes, especially in plasma lipoprotein and cholesterol levels³⁹. In postmenopausal women, total cholesterol, LDL cholesterol and triglyceride levels are increased and HDL cholesterol is decreased compared with premenopausal women of the same age and BMI²⁰. Several studies have investigated relationships of lipid levels with depressive or anxiety disorders^{43, 28}. Possible explanations can be derived from several studies that showed how recurrent depressive disorder may have a biological link to low cholesterol by its association with altered central serotonergic functions²³. On the other hand some studies also showed no such association³⁸, or yielded inconsistent results^{35, 37}. Whether there is a causal relationship between altered lipid metabolism, thyroid dysfunction and recurrent depressive disorder in subgroup of postmenopausal women or vice-versa is unknown. As a preliminary step to this complex problem, we planned the study to delineate the relationship between comorbidity of recurrent depressive disorder and TSH and lipid profile dysfunction in post-menopausal women (PMW).

MATERIAL AND METHODS

To study whether there is increased prevalence of thyroid dysfunction and altered lipid metabolism in PMW with recurrent depressive disorder as compared to PMW without recurrent depressive disorder a cross sectional study was carried out at the out-patient department of Gynaecology and Psychiatry at SMS Medical College and Hospital, Jaipur. One hundred consecutive

postmenopausal patients with recurrent depressive disorder (age ranging from 45 to 60 years), diagnosed on the basis of ICD-10 research criteria were included in the experimental group. The diagnosis was confirmed by two psychiatrists, independently⁴⁵. The control group consisted of 100 non depressed PMW matched on the basis of age and socio-demographic variables. Subjects with significant physical or neurological illness, any evidence of comorbid psychiatric disorder other than recurrent depressive disorder and prior history of psychiatric illness, having history of psychiatric illness in first degree relative or history of receiving hormonal treatment were excluded from the study. The study was approved by the institutional ethics committee. Informed consent was taken from all the study participants.⁴⁴ The following tools were used in the study:

1. A specially designed pro forma to include socio-demographic details, psychiatric diagnosis (if any) and check-list of symptoms known to occur in postmenopausal syndrome.
2. Hindi version of Beck's depressive self-rating inventory for assessing and quantifying recurrent depressive disorder. This is a self-reporting scale for quantification of recurrent depressive disorder. It contains 21-items score of 0-3 of which 15 items deal with psychological symptoms and only 6 are concerned with somatic ones^{6, 7, 8}.
3. Biochemical Investigations: Over-night fasting blood sample of all the subjects were collected using aseptic technique from the ante-cubital vein. Serum separated lipid profile (total cholesterol, serum triglycerides, High density Lipoprotein (HDL), Low density Lipoprotein (LDL) and Very Low Density Lipoprotein (VLDL)) and Thyroid Stimulating Hormone (TSH) were assessed using Auto analyser (Selectra E and Micro Lab 300) and Automated – immunoassay analyser (Immulate 1000), by using commercially available reagents and kits. The procedure given in the manuals, accompanying the kits, were strictly followed⁵⁴. Cholesterol estimation was done by endpoint CHOD-POD Method⁴¹. Triglycerides were monitored by enzymatic endpoint GPO-POD Method¹², HDL was estimated by direct liquid enzymatic method⁴² whereas VLDL and LDL were calculated by Friedwalds formula. Thyroid stimulating hormone (TSH) was assessed by Chemiluminescence immunoassay.

Statistical Analysis

All the parameters were expressed as mean and standard deviation (SD). Chi – square test (χ^2) and Z test were used to compare both the groups. Correlation analysis was undertaken using Pearson correlation coefficients (r)⁵³. Results were considered significant when p – values were less than 0.05.

RESULTS

Table 1: Distribution of subjects studied

| Groups | Cases |
|---------------------------------------|------------|
| Depressed Post-Menopausal Women (PMW) | 100 |
| Non Depressed Post-Menopausal Women | 100 |
| Total subjects | 200 |

Table 2: Distribution according to age of postmenopausal women with recurrent depressive disorder and PMW without recurrent depressive disorder

| Age group (In years) | Depressed PMW | | Non Depressed PMW | |
|-------------------------|---------------|---------------|-------------------|---------------|
| | No. | % | No. | % |
| 45-49 | 35 | 35.00 | 33 | 33.00 |
| 50-54 | 19 | 19.00 | 23 | 23.00 |
| 55-60 | 46 | 46.00 | 44 | 44.00 |
| Total | 100 | 100.00 | 100 | 100.00 |

$\chi^2 = 0.484$ D.F. =2 P > .05 NS

Both the groups were of comparable age group.

Table 3: Distribution of postmenopausal women with recurrent depressive disorder on the basis of Beck's score

| Beck's Score | Depressed PMW | |
|---------------------------------|---------------|---------------|
| | No. | % |
| Normal(0-9) | 0 | 0.00 |
| Mild depression(10-15) | 46 | 46.00 |
| Moderate depression(16-23) | 44 | 44.00 |
| Severe depression(24 and above) | 10 | 10.00 |
| Total | 100 | 100.00 |

Table 4: Comparison of Beck's Score of postmenopausal women with recurrent depressive disorder and PMW without recurrent depressive disorder

| Parameter | Depressed PMW (N=100) | Non depressed PMW (N=100) | P-value | Significance |
|--------------|--------------------------|------------------------------|---------|--------------|
| | Mean + SD | Mean + SD | | |
| Beck's Score | 17.46 + 5.84 | 4.14 + 2.17 | < .001 | HS |

Table 5: Comparison of serum TSH of postmenopausal women with recurrent depressive disorder and PMW without recurrent depressive disorder

| Parameter | Depressed PMW (N=100) | Non depressed PMW (N=100) | P-value | Significance |
|--------------------|--------------------------|------------------------------|---------|--------------|
| | Mean + SD | Mean + SD | | |
| TSH (μ IU/ml) | 5.19 + 4.62 | 3.08 + 1.72 | < .001 | HS |

Table 6: Correlation between Beck's Score and Serum TSH of postmenopausal women with recurrent depressive disorder and PMW without recurrent depressive disorder

| Group | R-value | P-value | Significance |
|-------------------|---------|---------|--------------|
| Non Depressed PMW | + 0.151 | > .05 | NS |
| Depressed PMW | + 0.707 | < .001 | HS |

Table 7: Comparison of lipid profile of PMW with recurrent depressive disorder and PMW without recurrent depressive disorder

| Parameter | Depressed PMW (N=100) | Non depressed PMW (N=100) | P-value | Significance |
|---------------------------|--------------------------|------------------------------|---------|--------------|
| | Mean + SD | Mean + SD | | |
| Total Cholesterol (mg/dl) | 208.02 + 56.88 | 180.26 + 41.33 | < .001 | HS |
| Triglyceride (mg/dl) | 147.06 + 72.00 | 137.52 + 70.15 | > .05 | NS |
| HDL (mg/dl) | 48.77 + 11.31 | 52.65 + 10.62 | < .05 | Sig |
| LDL (mg/dl) | 125.36 + 46.98 | 106.60 + 32.14 | < .001 | HS |
| VLDL (mg/dl) | 29.38 + 14.39 | 27.49 + 14.03 | > .05 | NS |

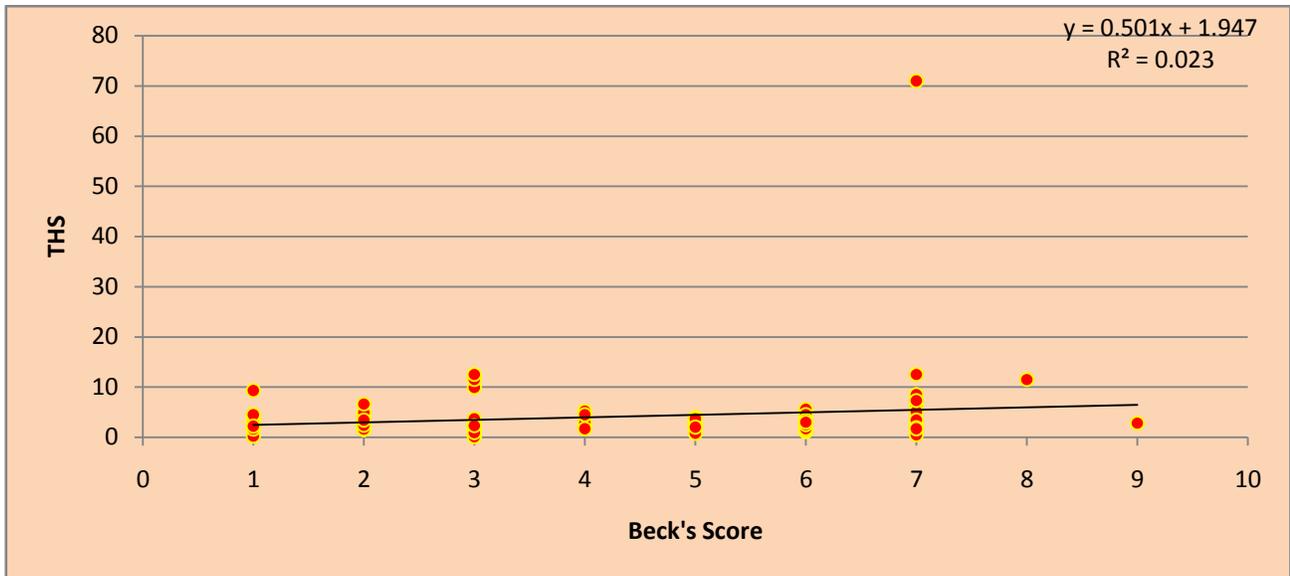


Figure 1: Correlation of serum TSH levels and Beck's score in postmenopausal women with recurrent depressive disorder and PMW without recurrent depressive disorder

In the present study, one hundred undepressed postmenopausal women, without a history of psychiatric disorders or endocrine illness were matched with one hundred depressed postmenopausal women (study group), sociodemographic variables were also included in the study (Table: 1). When comparison of sociodemographic characteristic of postmenopausal women with recurrent depressive disorder and PMW without recurrent depressive disorder was done it was found that in both the groups, most subjects were married and were living with spouse. Maximum subjects were housewives with primary education and having a monthly family income up to Rs.10000⁵².The subjects were from nuclear family, belonging to Muslim religion and of urban background. Majority of subjects were in the age group of 55 to 60 years (Table 2). The depressed PMW and non depressed PMW were comparable on sociodemographic variables. Our findings are in accordance with those of³³, they didn't find relationship between depression and economic status among the postmenopausal women⁴⁰. Table 3 suggests that among the depressed women 46% were mildly depressed whereas 44% were moderately depressed. Although only 10% women were severely depressed. Our data suggested significantly higher Beck's score in depressed PMW as compared to controls (Table 4). In depressed PMW the mean Beck's score was 17.46 + 5.84 while that of non depressed PMW was 4.14 + 2.17 .Depressed PMW had significantly higher Beck's score than that of the control group³⁴. Among the Depressed PMW, Beck's score mildly depressed females was between 10-15, moderately depressed women had a Beck's score of 16-23 and severely depressed women had a Beck's score of 24 and above (Table 3).

The results obtained also confirmed the role TSH in depressive disorders in post-menopausal women. As depicted in table 5, TSH Levels were significantly high in postmenopausal women with recurrent depressive disorder (P-value < .001). Mean serum TSH values of depressed PMW (5.19 + 4.62 μ IU/ml) as compared to control subjects (3.08 + 1.72 μ IU/ml)³⁶. The results obtained clearly suggests highly significant positive correlation between Beck's score and TSH levels in depressed PMW (Table 6 and figure 1). Depressed PMW has a high R-value (+ 0.707) and highly significant P-value of < .001. Whereas undepressed PMW had an R-value of + 0.151 and insignificant p-value of > .05. The data also depicts that serum total cholesterol and LDL levels were significantly higher and HDL levels were significantly lower in depressed PMW². The levels of triglycerides and VLDL were almost similar in both the groups (Table 7).The mean total cholesterol values of depressed PMW (208.02 + 56.88 mg/dl) were significantly higher (P < .001) as compared to healthy PMW (180.26 + 41.33 mg/dl). Triglyceride were assessed as (mg/dl) 147.06 + 72.00mg/dl in depressed PMW as compared to control which had a value of 137.52 + 70.15mg/dl which shows insignificant results with a p-value of > .05³¹. The mean value of HDL and LDL were 48.77+11.31mg/dl and 125.36+46.98mg/dl respectively in depressed PMW which was significant as compared to control. The mean value of VLDL was 29.38 + 14.39mg/dl in depressed PMW as compared to non-depressed PMW which had a value of 27.49 + 14.03mg/dl which was insignificant with P-value of > .05.

DISCUSSION

Depression is highly prevalent with approximately 10% of the population experience a clinically significant depression and the cases of acute to chronic depression are increasing in frequency³. The lifetime rate of major depression is two to three times higher in women than men. Women are prone to depression during times of reproductive hormone changes such as puberty, the postpartum period, the premenstrual phase of the menstrual cycle and the perimenopause and postmenopause⁵. Recurrent depressive disorder, one of the major health problems, is common among middle aged women who experience menopause. Female susceptibility to mood disorder appears to be influenced by reproductive system function^{14, 25}. Henceforth, this study was planned to develop an understanding towards the underlying mechanism and to find out if there is any association of lipid profile and thyroid status with recurrent depressive disorder in menopausal women.

Several investigations have established that the depressed PMW experienced more climacteric symptoms as compared to the non-depressed PMW. The most characteristic symptoms of the menopausal syndrome are hot flushes, sleep disturbances and mood changes resulting from the hyperactivity of the mid brain hypothalamic pituitary axis, and from changes in the central nervous system¹⁹. Depression is not a universal symptom at the time of menopause. However, studies have shown that a significant number of women experience depression and psychological symptoms in association with menopause. Currently, it appears that the etiology for depression during periods is multifactorial, including social psychological influences combined with biologic (sex steroid) factors¹⁶.

Several researches have confirmed the role of sex hormones in menopause. It has been established earlier that the menopause transition is a period of marked hormone instability and the later phases of the transition are characterised by a steep increase in FSH levels, followed by a dramatic decline in estradiol level²². Although another study has shown that the levels of both of these hormones are then thought to stabilise as women enter the postmenopause¹³, but despite this stabilization these hormone may influence depression status during postmenopausal condition. The decreased circulating estrogen levels during menopause have also been linked to loss of libido, fatigue and an increase in depressive symptoms^{4, 24} (Artt W, 2006 and Freeman MA, 2002). In our study we have also established the fact that depressed PMW had the mean Beck's score was 17.46 + 5.84 while that of non depressed PMW was 4.14 + 2.17. The Beck's score is obtained by undergoing 21-question multiple-choice self-report inventory, one of the most widely used

psychometric tests for measuring the severity of depression²¹. This test is known as Beck Depression Inventory and higher total scores indicate more severe depressive symptoms. Depressed PMW had significantly higher Beck's score than that of the control group. Among the Depressed PMW, 46% females were mildly depressed (Beck's score was between 10-15), 44% were moderately depressed (Beck's score was between 16-23) and only 10% were severely depressed (Beck's score was 24 and above). The results clearly indicate that postmenopausal women face depression to some extent although chances of severe depression is really low.

Postmenopausal women with recurrent depressive disorder have significantly higher TSH level as compared to postmenopausal women without recurrent depressive disorder. Hence, there was statistically significant association between TSH levels and recurrent depressive disorder in PMW³⁰. Our results are in the accordance with an earlier study by Schindler⁸ which found that even mild thyroid failure can have a number of clinical effects such as recurrent depressive disorder, memory loss, cognitive impairment and a variety of neuromuscular complaints. In the present study mean serum TSH values of depressed PMW (5.19 + 4.62 μ IU/ml) were significantly higher ($P < .001$), as compared to healthy control subjects (3.08 + 1.72 μ IU/ml). In another study¹⁵, it was demonstrated that there is an increase of elevated thyroid stimulating hormone (TSH) with age. This occurs more frequently in women than in men.

This study also illustrates that highly significant positive correlation was found between Beck's score and TSH levels in depressed PMW. Depressed PMW has a high R-value (+ 0.707) and highly significant P-value of $< .001$. Thus establishing a fact that the TSH level levels are directly correlated to the depression in post-menopausal women.

There was a significant difference in level of cholesterol, LDL and HDL in control and depressed PMW. Serum total cholesterol and serum LDL were significantly higher and serum HDL levels were significantly lower while serum triglyceride and VLDL levels were comparable in both the groups. The mean total cholesterol values of depressed PMW (208.02 + 56.88 mg/dl) were significantly higher ($P < .001$) as compared to healthy PMW (180.26 + 41.33 mg/dl). Our results are in accordance with those of Das *et al*, they evaluated the serum total cholesterol levels in depressed subjects and showed that there is significant elevation of serum total cholesterol in depressed patients compared with normal controls and this persists even after controlling for the confounders¹⁸. Another study by Gupta *et al*. suggested that measurement of serum cholesterol levels may actually indicate towards hypothyroidism in depressed

subjects²⁷. Our findings are also in favour of the one conducted by Paterson ME *et al*, 1979 they evaluated that postmenopausal women had significantly higher levels of serum cholesterol than the premenopausal women⁴⁹. Brown in 2004 found that greater levels of depressive symptoms were associated with lower cholesterol levels in the postmenopausal women¹¹.

In another similar study it was found that high triglycerides levels were associated to higher rates of sweating and depression among PMW¹⁷. In 1989 Karen had also found that in women who had a menopause and did not receive hormone replacement therapy, serum levels of high density lipoprotein (HDL) cholesterol declined as compared with those of premenopausal controls and levels of low density lipoproteins (LDL) cholesterol is increased¹⁰. The results obtained in this study are also in accordance with these studies as the mean value of HDL was 48.77+11.31mg/dl and LDL was 125.36+46.98mg/dl in depressed PMW which was significant as compared to control. Our results are in favour of the study done by Papakostar GI *et al*, 2003. They found relationship between hypercholesterolemia and poor outcome in the treatment of major depressive disorder. Our study clearly indicates an association between cholesterol, low and high density lipids and depression in post-menopausal women⁴⁷.

Another such study has reported that when Postmenopausal women were categorized into normal controls and those having anxiety disorders and depressive disorders, no significant differences were found in lipid concentrations among the 3 groups²⁷.

Although the underlying mechanism is not yet clear but many researchers suggest that main reason for depression in middle age women is due to lower secretion of estrogen after the menopause⁵⁵. Maes reported that changes in serum lipid comparison may be related to suicide, major recurrent depressive disorder and immune inflammatory responses³⁸. Their findings suggest that major recurrent depressive disorder is accompanied by reduced formation of cholesteryl esters and perhaps by impairment of reverse cholesterol transport. The latter is reportedly accompanied by lower serum high density lipoprotein cholesterol (HDL – C). They concluded major recurrent depressive disorder is accompanied by lower serum HDL–C or by abnormal levels of serum total cholesterol, triglycerides, low density lipoprotein C.

In keeping with the effect of higher androgens, higher estradiol levels associated with higher triglycerides, ApoB and lower HDL-cholesterol and ApoA. In 2005 Mudali recently reported a strong positive association between estrone and total cholesterol and triglycerides among postmenopausal women with significant carotid atherosclerosis⁴². Contradictory to this, Ossewaarde *et al*

demonstrated a significant positive association between plasma estrone and HDL-cholesterol, and a negative association with triglycerides and very low-density lipoprotein-cholesterol in a small sample of healthy postmenopausal women⁴⁶.

Schindler in his study found increased serum total cholesterol and low density lipoprotein cholesterol as well as reduced levels of high density lipoprotein as well as hypothyroidism⁵¹. Therefore, he recommended routine screening of thyroid function in the climacteric period to determine subclinical thyroid and overt hypothyroidism.

Since depression and emotional symptoms occur in many women during the post-menopausal years, it is important to establish the mechanism behind the disorder. Taken together more such studies need to be done to understand the role of various biological moieties in the post-menopausal symptoms.

CONCLUSION

The findings of our study suggest that comorbidity between depression and altered metabolism occurs frequently. It may be clinically important to screen Depressed PMW for altered lipid metabolism and thyroid dysfunction. Further work needs to be done to clarify if there is a causal relationship between recurrent depressive disorder and metabolism in PMW.

REFERENCES

1. Alexopoulos G S, Kalz I R, Reynolds C F III, Carpenter D, Doherty J P. The expert consensus guideline series: Pharmacotherapy of depressive disorders in older patients. Post graduate medicine special report.2001
2. Anderson E, Hamburger S, Liu J H, Rebar R W. Characteristics of menopausal women seeking assistance. Am J ObstetGynecol 1987; 156: 428-33.
3. Archer J S. Relationship between estrogen, serotonin and recurrent depressive disorder. Menopause .1999; 6: 71-8.
4. Artt W. Androgen therapy in women .Eur J Endocrinol. 2006; 154:1-11.
5. Beck AT, Rial WY, Ricketts K. Short form of recurrent depressive disorder inventory: cross validation. Psychol Rep.1974; 34(3):1184-6.
6. Beck, AT, Steer RA. Internal consistencies of the original and revised Beck Recurrent depressive disorder Inventory. J ClinPsychol 1984; 40(6):1365-7.
7. Beck, Ward, Mendelson, Mock and Erbaugh. An inventory for necologic care.1961; 4th ed., St. Louis: Mosby.
8. Beck, Ward, Mendelson, Mock, Erbaugh .An inventory for measuring recurrent depressive disorder. Arch Gen Psychiat 1961; 4: 561-571.
9. Bobak, IM, Jensen MD, Zalar MK. Maternity and gynecologic care 1990; 4th ed., St Louis: Mosby.
10. Bromberger, JT, Matthes KA, Schott LL. Depressive symptoms during the menopausal transition: the study of women's health across the nation (SWAN). J Affect Disord 2007; 103: 267-72.

11. Brown, ES, Varghese, FP and McEwen, BS. Association of depression with medical illness: does cortisol play a role? *Biological Psychiatry*. 2004; Vol 55: 1; 1-9.
12. Buccolo G. Quantitative determination of serum triglyceride by use of enzymes. *Clin Chem* 1973; 19(5):476-482.
13. Burger HG, Dudley EC, Robertson DM and Dennerstein L. Hormonal changes in the menopause transition. *Recent Prog Horm Res*. 2002; 57:257-75.
14. Burt VK and Stein K. Epidemiology of depression throughout the female life cycle. *J Clin Psychiatry*. 2002; 63 (Suppl 7) : 9-15
15. Canaris G J, Manowitz N R and Major G. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000; 160: 526 -34.
16. Chang ER. A study on factors that affect ego-identity and recurrent depressive disorder of middle-aged women. Masters thesis. 2000: Seoul Theological University, Seoul.
17. Chedraui P, Hidalgo L, Chanez D, Morocho N, Alvarado M and Huc A. Menopausal symptoms and associated risk factors among PMW screened for the metabolic syndrome. *Arch Gynecol Obstet*. 2007; 275:161-168
18. Chien Chih C, Tiao Lai H. Association of serum Lipid Profiles with Depressive and Anxiety Disorders in Menopausal Women. *Chang Gung Med J* 2006; 29: 325-30.
19. Chowta N K, Sabastian J and Chowta M N. Comparative study of menopausal symptoms in postmenopausal and Perimenopausal women. *Journal of Clinical and Diagnostic Research*. 2008 Aug; (2): 959-962.
20. Das P P, Malhotra S, Chakrabarti S and Sharma S. Elevated total cholesterol in severely depressed patients: Role in cardiovascular risk? *World J Biol Psychiatry*. 2009.
21. De Kleijn MJ, VanderSchouw YT, Banga JD, Vander GY. The effect of menopause on risk factors for ischemic diseases. *Ned Tijdschr Geneesk* 1996; 140: 478-482.
22. Dennerstein L, Lehert P, Burger H G and Guthrie J R. New findings from non-linear longitudinal modelling of menopausal hormone changes. *Hum Reprod Update*. 2007.
23. Ellen WF, Mary DS, Hui L, Deborah BN. Association of hormones and menopausal status with depressed mood in women with no history of recurrent depressive disorder. *Arch Gen Psychiatry* 2006; 63 (4): 375-382.
24. Engelberg H. Low serum cholesterol and suicide. *Lancet* 1992; 339: 727-9.
25. Freedman M A. Quality of life and menopause: The role of estrogen. *J Women Health* .2002; 11:703-18.
26. Gibbs Z, Lee S, Kulkarni, J. Factors associated with depression during menopausal transition. *Women's Health Issues*. 2013 Sep-Oct; 23(5):e301-7. doi: 10.1016/j.whi.2013.07.001
27. Gupta S, Saha P K and Mukhopadhyay A. Prevalance of hypothyroidism and importance of cholesterol estimation in patients suffering from major depressive disorder. *J Indian Med Assoc*. 2008; 106 : 240-2
28. Hadine J, Claudio NS, Lee SC. Assessment and treatment of hot flushes and menopausal mood disturbance. *Psychiatr Clin N Am* 2003; 26: 563-580.
29. Holland WW, Detels R, Knox G, Fitzsimons B, Gardner L. *Oxford textbook of public health*. 1991; 2nd ed, Oxford university press, 170-172.
30. Huang TL. Serum Lipid profiles in major recurrent depressive disorder with clinical subtypes, suicide attempts and episodes. *J Affect Disord* 2005; 86: 75-9.
31. Karen AM, Elaine M, Lewis HK, Sheryl FK, Arlene WC, Rne RW. Menopause and Risk Factors for Coronary Heart Disease. *N Engl J Med* 1989; 321(7): 641-646.
32. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994; 51: 8-19.
33. Kim SS. The associated factors with the recurrent depressive disorder of middle-aged women living in a city. Unpublished doctoral dissertation. 2000; Chosun University, Kwangju.
34. Kwon SH, Kim YJ, Moon KN, Kim IS, Park KJ, Park CW, Bae JE, Song AR, Yeo JH, Jung ES, Jung HM. The climacteric symptoms and recurrent depressive disorder in middle-aged women. *Korean J Women Health Nurs* 1995; 2(2): 235-243.
35. Lee Y W. Recurrent depressive disorder in postmenopausal women. *Taihan Kanho Hakhoe Chi* 2003; 33(4):471-477.
36. Lepine JP, Bouchez S. Epidemiology of recurrent depressive disorder in the elderly. *Int Clin Psychopharmacol* 1998; 13: S7 - S12.
37. Lindberg G, Larsson G, Setterlind S, Rastam L. Serum lipids and mood in working men and women in Sweden. *J Epidemiol Commun Health* 1994; 48: 360-3.
38. Maes M, Smith R, Christophe A, Vandoolarghe E, Vangastle A, Neels H, Demendts P, Wauters A, Meltz HY. Lower serum high density lipoprotein cholesterol (HDL-C) in major recurrent depressive disorder and in depressed men with serious suicidal attempts: relationship with immune inflammatory markers. *Acta Psychiatrica Scandinavia* 1997; 95(3): 212-221.
39. Markovitz J H, Smith D, Raczynski J M, Oberman A, Williams O D, Knox S, Jacobs DR . Lack of relations of hostility, negative affect, and high-risk behavior with low plasma lipid levels in the Coronary Artery Risk Development in Young Adults Study. *Arch Intern Med*. 1997; 157: 1953-9.
40. McCallum J, Simons L, Simons J, Friedlander Y. Low serum cholesterol is not associated with recurrent depressive disorder in the elderly: data from an Australian community study. *Aust NZ J Med*. 1994; 26:561-4.
41. Milan M T, Jelena D, Sanja M, Tihomir M and Bratislava T. Influence of red clover-derived isoflavones on serum lipid profile in postmenopausal women. *J Obstet Gynaecol Res*. Dec 2009; 35(6):1091-1095.
42. Mudali S, Dobs AS, Ding J, Jingzhong D, Cauley JA, Moyses S and Golden SH. Endogenous postmenopausal hormones and serum lipids: the Atherosclerosis Risk in Communities Study. *Journal of Clinical Endocrinology and Metabolism*. 2005; 90: 1202-1209.
43. Naito H K: Cholestrol. *Clin Chem*. 1984; 1194-11206.
44. Naito H K: HDL Cholestrol. *Clin Chem*. 1984; 1207-1213.

45. Olusi S O, Fido A A. Serum Lipid Concentration in patients with major depressive disorder. *Biol Psychiatry*. 1996; 40:1128-31.
46. Ossewaarde ME, Bots ML, van der Schouw YT, Thijssen JHH, Westerveld T, de Jong FH and Grobbee DE. Plasma and urinary sex hormones are differently related to lipids in healthy postmenopausal women. *Maturitas*. 2003; 44: 181–187
47. Papakostas GI, Petersen T, Sonawalla SB, Merens W, Iosifescu DV, Alpert JE, Fawa M and Nerenberg AA. Serum cholesterol in treatment – resistant depression. *Neuropsychobiology*. 2003; 47(3): 146 – 51.
48. Parry B L, Meliska C J, Martinez L F, Basavaraj N and Zirpoli G G. Menopause: neuroendocrine changes and hormone replacement therapy. *J Am Med Womens Assoc*. 2004 Spring; 59(2): 135-45.
49. Paterson ME, Sturdee DW, Moore B and Whitehead TP. The effect of menopausal status and sequential mestranol and norethisterone on serum cholesterol, triglyceride and electrophoretic lipoprotein patterns. *Br J Obstet Gynaecol*. 1979 Oct; 86(10): 810-5.
50. Schindler TH, Campisi R, Dorsey D, Prior JO, Olschewski M, Sayre J, Schelbert HR. Effect of hormone replacement therapy on vasomotor function of the coronary microcirculation in post-menopausal women with medically treated cardiovascular risk factors. *Eur Heart J*. 2009 Apr; 30(8):978-86. Doi: 10.1093/eurheartj/ehp013. Epub 2009 Feb 26
51. Shin M H. A study on the relationship between the climacteric symptoms and recurrent depressive disorder in menopausal women who have received hormonal replacement therapy. Master thesis.2001; Soonchunhyang University, Onyang.
52. Stevenson J C, Crook D, Godsland I F. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis*. 1993; 98:83-90.
53. Stevenson J C, David C and Ian F G. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis*.1993; 98(1): 83-90.
54. Sung, M H. An analysis of the relationship between climacteric symptoms and recurrent depressive disorder of middle-aged women. *Korean J Women Health Nurs*.2000; 6(4): 465-476.
55. Soares C N. Newyork, Arlington, V A: American Phyciatric Publishing; 2004. Perimenopause related mood disturbance: An update on risk factors and novel treatment strategies available. In: meeting programs and abstracts. Psychopharmacology and reproductive transitions symposium. American psychiatric association 157th annual meeting; May 1-6, 2004; pp51-61
56. Wood N F and Mitchell E S. Patterns of depressed mood in midlife women: Observation from the Seattle midlife women’s health study. *Res Nurs Health*. 1996; 19: 111-123.

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