Original Article

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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Received Date: 10/02/2016 Revised Date: 13/03/2016 Accepted Date: 18/04/2016

Access this article online	
Quick Response Code:	Website: www.statperson.com
	DOI: 01 May 2016

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 disturbances[26]. 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

How to site this article: Aditi Ranawat, Maheep Sinha, Ram Kumar Solanki. Comorbidity of recurrent depressive disorder with thyroid dysfunction and altered lipid metabolism in postmenopausal women: A case-control study. *International Journal of Recent Trends in Science and Technology* May 2016; 19(1): 05-12 http://www.statperson.com (accessed 02 May 2016).

at some point during menopause[56]. 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 levels[9]. The psychological symptoms such as depression, loneliness and despair usually persist even after cessation of hot flashes, fainting, headache, palpitation and insomnia[32]. It is well documented that recurrent depressive disorder occurs about 2 times more frequently in women than in men[30] and may increase during time of menopause[3]. Studies have also shown that recurrent depressive disorder increases mortality and morbidity[1]. 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 infarction[48]. In 1989 Karen suggested that natural menopause affects lipid metabolism unfavourably[29]. Menopause, with its well-known hormonal profile, is associated with adverse metabolic changes, especially in plasma lipoprotein and cholesterol levels[39]. 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 BMI[20].

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 functions[23]. On the other hand some studies also showed no such association[38], 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, independently[45]. 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 post-menopausal 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 (Immulite 1000), by using commercially available reagents and kits. The procedure given in the manuals, accompanying the kits, were strictly followed[54]. Cholesterol estimation was done by endpoint CHOD-POD Method[41]. Triglycerides were monitored by enzymatic endpoint GPO-POD Method[12], HDL was estimated by direct liquid enzymatic method[42] 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 ($\chi 2$) 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 ofpostmenopausal 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**

χ^2 = 0.484 D.F. =2 P > .05 NS

Both the groups were of comparable age group.

Table 3: Distribution ofpostmenopausal 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 disorderand PMW without recurrent depressive disorder

Parameter	Depressed PMW (N=100) Mean + SD	Non depressed PMW (N=100) Mean + SD	P-value	Significance
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) Mean + SD	Non depressed PMW (N=100) Mean + SD	P-value	Significance
TSH (µIU/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) Mean + SD	Non depressed PMW (N=100) Mean + SD	P-value	Significance
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

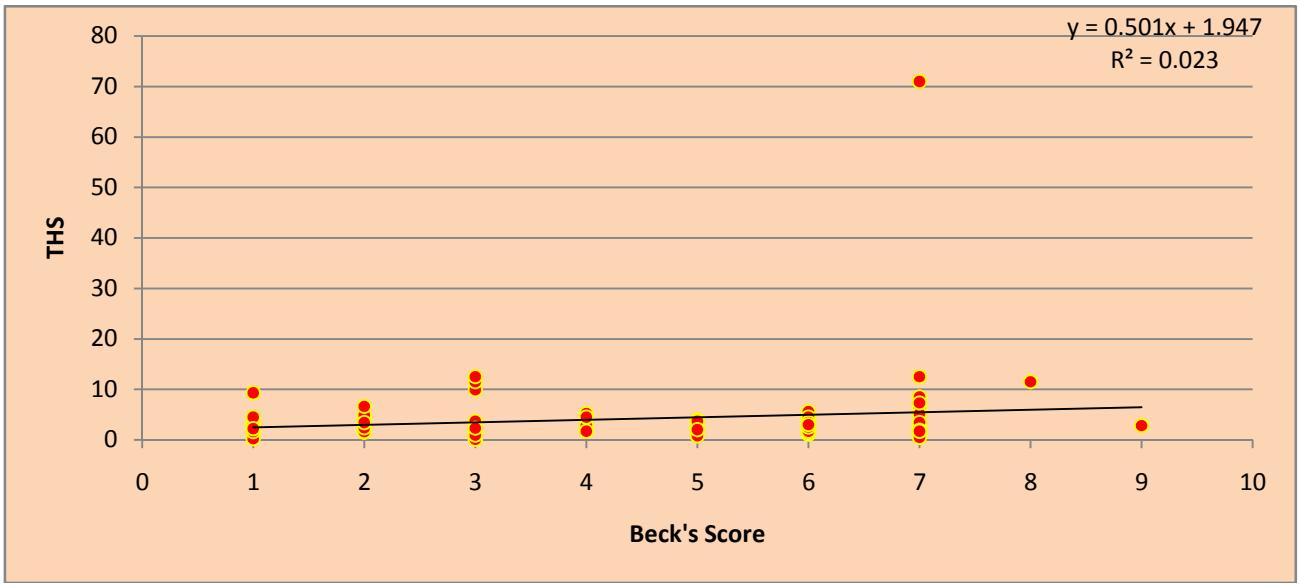

Figure 1: Correlation of serum TSH levels and Beck's score in postmenopausal women with recurrent depressive disorder and PMW without recurrent depressive disorder

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.10000[52].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 of[33], they didn't find relationship between depression and economic status among the postmenopausal women[40]. 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 group[34]. 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 µIU/ml) as compared to control subjects (3.08 + 1.72 µIU/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 anR-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 PMW[2]. 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 > .05[31]. The mean value of HDL and LDLwere 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 frequency[3]. 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 postmenopause[5]. 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 system[19]. 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) factors[16].

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 level[22]. Although another study has shown that the levels of both of these hormones are then thought to stabilise as women enter the postmenopause[13], 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 depression[21]. 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 post-menopausal 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 PMW[30]. Our results are in the accordance with an earlier study by Schindler[8] 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 µIU/ml) were significantly higher (P<.001), as compared to healthy control subjects (3.08 + 1.72 µIU/ml). In another study[15], 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 confounders[18].Another study by Gupta *et al*. suggested that measurement of serum cholesterol levels may actually indicate towards hypothyroidism in depressed

subjects[27]. 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 women[49]. Brown in 2004 found that greater levels of depressive symptoms were associated with lower cholesterol levels in the postmenopausal women[11].

In another similar study it was found that high triglycerides levels were associated to higher rates of sweating and depression among PMW[17]. 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 increased[10]. 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 women[47].

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 groups[27].

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 menopause[55]. Maes reported that changes in serum lipid comparison may be related to suicide, major recurrent depressive disorder and immune inflammatory responses[38]. 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 atherosclerosis[42]. 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 women[46].

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 hypothyroidism[51]. 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.

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Source of Support: None Declared
Conflict of Interest: None Declared