Impacts of menopause hormone therapy on mood disorders among postmenopausal women

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ABSTRACT

Objective: This study aimed to explore the modulatory effects of menopause hormone therapy (MHT) on mood disorders among postmenopausal women.

Methods: A cross-sectional study was conducted to recruit postmenopausal women, including patients (arranged MHT for over 3 years as the medication group) and non-MHT controls. All participants were asked to respond to the Center for Epidemiological Studies Depression Scale (CES-D) and Generalized Anxiety Disorder Screener (GAD-7) questionnaires to assess their depression and anxiety status.

Results: A total of 230 cases from the two groups were determined based on propensity score matching analysis by matching the menopausal age and menopausal durations. We found that MHT served as a favorable modulator in the depression status of postmenopausal women. Among the four factors of the CES-D questionnaire, our data indicated that the differences between the two groups fell primarily into two aspects: depressive emotion, and somatic symptoms or retarded activities. MHT was mainly involved in improving the depression of overweight women. However, no substantial effects of MHT were observed on the regulation of anxiety.

Conclusion: Postmenopausal women, especially the overweight population, who have experienced MHT exhibited an improved depressive status but not their anxiety condition.

Introduction

Menopause is a natural physiological process of women. From the perimenopausal period, sex hormone variation enables women to suffer from a series of problems, such as abnormal uterine bleeding, menopausal symptoms, urogenital atrophy and metabolic diseases in older women. This has posed severe detriments for women’s health and quality of life [1]. Women tend to develop mood disorders in periods with apparent fluctuations in sex hormones, such as premenstrual and perimenopausal periods [2]. Besides, they have a higher chance to suffer from mood disorders than men [3]. The primary forms of mood disorders include anxiety and depression. Under the mutual influence of various menopausal symptoms, women are susceptible to emotional problems, which may be more severe with a higher risk of recurrence [4,5]. For example, compared with childbearing age, perimenopause patients are two to four times more likely to develop mood disorder [6]. Depression has been regarded to be one of the three dominating causes of the disease burden by the World Health Organization in 2030 [7]. The risk factors of depression in women are different from those in men, among which the roles of perceived poor health and obesity cannot be neglected [8]. Emotional disorders can aggravate during the menopausal transition and early menopause. The data from a longitudinal cohort of aging middle-aged women in China (the Peking Union Medical College Hospital Aging Longitudinal Cohort of Women in Midlife (PALM) study) demonstrated that depressive symptoms appeared more frequently than anxiety. The prevalence of depressive symptoms augmented gradually from the transitional period of menopause to the early stage of menopause. Meanwhile, although the prevalence of anxiety symptoms increased slightly as well, the change was not so obvious [9]. Another study of perimenopausal people indicated that the incidence of depression and anxiety was basically consistent with the conclusion of the PALM cohort [10].
was a large community-based study of ovarian aging and the findings revealed that depression was common during menopausal transition and postmenopausal stage [6].

Recently, a study of 172 participants has validated the effectiveness of 12-month intervention of menopause hormone therapy (MHT) in preventing depressive symptoms during the menopausal transition and early menopause. Previous evidence also supported that estrogen supplementation could directly or indirectly alleviate depression [11,12]. Anxiety is defined as the expectation of future threats or worries about potential situations in daily life [13]. At present, the perspectives about the actions of MHT on anxiety are not consistent. A clinical trial of the Kronos Early Estrogen Prevention Cognitive and Affective Ancillary Study (KEEPS-cog) aimed to explore the emotional impact of MHT on postmenopausal women. Researchers found that women’s symptoms of depression and anxiety have been relieved after 48 months of treatment [14]. However, another study held opposite views and found no significant improvement in the effects of MHT on anxiety after a 6-month intervention [15]. MHT has been carried out in China for more than 20 years [16], but most studies have elucidated the underlying function of estrogen in improving mood conditions during menopausal transition or early menopause. However, limited studies are exploring the emotional regulation of long-term MHT in postmenopausal women in China.

Therefore, we have recruited postmenopausal women with or without MHT for at least 3 years. A questionnaire survey on anxiety and depression was conducted to explore the modulatory effects of MHT on menopause-related mood disorders based on a comprehensive analysis, including the generalized linear regression model (GLM) and propensity score matching (PSM).

Methods

Study design

The postmenopausal participants were recruited voluntarily during regular check-ups. They were involved in MHT management in the outpatient clinic from January 2019 to June 2021. The inclusion criteria for MHT cases consisted of: patients who were defined in the stage of at least +1C in accordant with the Stages of Reproductive Aging Workshop (STRAW) +10 classification [17]; postmenopausal women who received MHT for at least 3 years; and the MHT regimen conformed to the guidelines and was reviewed by two gynecologic experts. The exclusion criteria included: the use of psychotropic drugs in the past half a year; and no history of major diseases affecting daily life. The control cases without MHT were mainly recommended by the members of the medication group (people with similar menopausal age, place of residence and education level), and their postmenopausal time met the aforementioned requirements.

The formulation of the therapeutic regimen in this study has followed the principles of the International Menopause Society (IMS) consensus in 2016 [18] and the guidelines for menopausal management and MHT in mainland China. A personalized medication plan for these postmenopausal women was developed according to their age and annual physical examination results. On the one hand, the use of progesterone depended on the status or presence of the uterus, and oral natural progesterone, such as oral micronized progesterone and dydrogesterone, has been applied in the past 10 years. On the other hand, the dosage and type of estrogen for these patients relied mainly on their age of menopause and postmenopausal time. In detail, one-third of the 115 patients included in the medication group have been treated for more than 10 years, and at present most of them have been receiving transdermal estrogen therapy. At the same time, tibolone, Progynova (estradiol valerate tablets, 0.5–1 mg per day) or transdermal estrogen (0.5–1 caliper per day) were arranged for those who have been menopausal for 5–10 years. In the group with menopausal duration of fewer than 5 years, estradiol valerate tablets (2 mg) and Femoston (complex packing estradiol tablets/estradiol and dydrogesterone tablets, 2/10 mg) were used for women whose menopausal age was younger than average; conversely, the remaining patients were treated with the sequential hormone replacement regimens for 1–2 years, followed by the continuous hormone replacement regimens.

The research program has been approved by the Ethics Committee of Peking Union Medical College Hospital (ethics: S-K1525). The completion and submission of the questionnaire meant that the participants agreed to participate. The answer could be terminated unconditionally at any time. Our questionnaire was formed from 27 items of the Center for Epidemiological Studies Depression Scale (CES-D) [19] and the Generalized Anxiety Disorder Screener (GAD-7) [20], including age, education, menopausal age, duration of MHT and other related personal details. To verify the completeness and structure of the questionnaire, we invited 10 postmenopausal women (five postmenopausal women who have received MHT and five non-MHT women) to conduct a presurvey after being reviewed by two gynecological endocrinologists.

The CES-D questionnaire is adopted to identify the depression status in the general population. Recently, it has been widely applied to evaluate the relationship between menopausal transition and depressive disorder [21]. This questionnaire has already been validated by a research team from the Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences based on 16,047 community participants (age range 11–100 years) in 21 provinces in China, and it is concluded that CES-D questionnaire is applicable with good reliability and validity across all ages [22]. Twenty projects of this questionnaire are applied to assess the frequency of symptoms and behaviors over the past 7 days. The main index is the total score, where total scores ≤15 points are regarded as no depressive symptoms, 16–19 points as possible depressive symptoms and ≥20 points as depressive symptoms. The GAD-7 questionnaire serves as one of the most widely used self-rating anxiety scales in clinical practice [23]. It mainly focuses on how the interviewees were troubled by each symptom in the past 2 weeks. The evaluation index is the total score as well, where 0–4 points are defined as normal, 5–9 points as mild
anxiety (can be self-regulated), 10–14 points as moderate anxiety (unable to self-adjust and need to see a doctor for help) and 15–21 points as severe anxiety (recommended for formal psychiatric specialist). The body mass index (BMI) is divided into two grades according to the standards of the Department of Disease Control and Prevention of the Ministry of Health of China [24]: BMI < 24 kg/m² (non-overweight) and BMI ≥ 24 kg/m² (overweight).

**Data collection**

The online questionnaire system (https://www.wjx.cn/) was introduced to assist in completing the survey to ensure the integrity of the questionnaire, which could be submitted when all questions were finished. Besides, the data were extracted automatically to avoid typing errors. It is also worth mentioning that the paperless questionnaire helped a lot to avoid paper waste. During the whole process, two researchers were responsible for checking the reliability and integrity of all of the collected information. In the following analysis, PSM was performed to minimize the bias [25] by matching the menopausal age and duration of menopause between the MHT-treated and non-MHT groups at the ratio of 1:1.

**Statistical analysis**

PASS software (version 11.0; NCSS Statistical Software) was adopted to calculate the appropriate sample sizes required for the two groups (α = 0.05, β = 0.20 and statistical power = 0.80) with a 1:1 allocation rate between the medication and control groups and a possible invalid questionnaire rate of 5%. Data were analyzed by SPSS Statistics software. The Shapiro–Wilk test with normality plots was used to evaluate the normal distribution. Data were expressed as numbers (percentages) for categorical variables and as mean ± standard deviation or median (interquartile range) for continuous variables. Student's t-tests or Mann–Whitney U-tests and chi-square tests were performed for comparisons between the two groups. At the same time, three models were developed based on the GLM by adjusting for different confounding factors, including age, education, BMI, age of menopause, and postmenopausal time, to further confirm the effects of MHT on mood disorders. Statistical differences were confirmed when p < 0.05.

**Results**

**Baseline characteristics of all participants**

As shown in the flow chart in Supplementary Figure 1, a total of 315 questionnaires were screened out according to the inclusion and exclusion criteria with complete baseline information. Significant differences in age, education and BMI levels were observed between the medication and control groups among all of the involved cases. More importantly, two menopause-related parameters of patients in the MHT group (earlier menopausal age and longer postmenopausal time) were dramatically different from those in the non-MHT group (Supplementary Table 1). To reduce the potential bias, PSM analysis was performed by matching the menopausal age and menopausal duration between the MHT and non-MHT participants. On this basis, 115 cases from each group were determined for further statistical analysis. The average age of the involved participants of both two groups was around 58 years (p = 0.623). Additionally, there existed no statistical difference in terms of the duration of menopause between the medication and non-MHT

| Characteristic                  | Non-MHT control group (n = 115) | MHT patient group (n = 115) | Total (n = 230) | p-Value |
|--------------------------------|---------------------------------|-----------------------------|-----------------|---------|
| Age (years)                     | 57.9 ± 5.9                      | 58.2 ± 6.3                  | 58.1 ± 6.1      | 0.623   |
| Education (%)                   |                                 |                             |                 | <0.001  |
| Uneducated                      | 1 (0.9)                         | 0 (0.0)                     | 1 (0.4)         | –       |
| Junior high or below            | 27 (23.5)                       | 2 (1.7)                     | 29 (12.6)       | –       |
| Senior high or undergraduate    | 85 (73.9)                       | 109 (94.8)                  | 194 (84.3)      | –       |
| Graduate or above               | 2 (1.7)                         | 4 (3.5)                     | 6 (2.6)         | –       |
| Age of menopause (years)        | 49.0 (4.0)                      | 48.0 (4.0)                  | 48.0 (4.0)      | 0.350   |
| Postmenopausal time (years)     | 9.3 (8.8)                       | 9.9 (7.8)                   | 9.9 (8.2)       | 0.344   |
| Medication time of MHT (years)  |                                 |                             |                 |         |
| 3–5                            | –                               | 34 (29.6)                   | –               | –       |
| 5–10                           | –                               | 55 (47.8)                   | –               | –       |
| >10                            | –                               | 26 (22.6)                   | –               | –       |
| Smoking (%)                     |                                 |                             |                 | 0.223   |
| Non-smoker                      | 108 (93.9)                      | 113 (98.3)                  | 221 (96.1)      | –       |
| Former smoker                   | 3 (2.6)                         | 2 (1.9)                     | 5 (2.2)         | –       |
| Current smoker                  | 4 (3.5)                         | 1 (0.9)                     | 5 (2.2)         | –       |
| Drinking (%)                    |                                 |                             |                 | 0.858   |
| Non-drinker                     | 91 (79.1)                       | 94 (81.7)                   | 185 (80.4)      | –       |
| Former drinker                  | 19 (16.5)                       | 16 (13.9)                   | 35 (15.2)       | –       |
| Current drinker                 | 5 (4.3)                         | 3 (2.6)                     | 8 (3.5)         | –       |
| BMI (kg/m²)                     | 24.2 (3.5)                      | 22.9 (4.3)                  | 23.4 (3.8)      | <0.001  |

Data expressed as numbers (percentages) for categorical variables and as median (interquartile range) for continuous variables, unless otherwise stated. Mann–Whitney U-tests for continuous variables and chi-square tests for categorical variables performed for comparisons between the two groups, unless otherwise stated. BMI, body mass index; MHT, menopausal hormone therapy.

*Data expressed as mean ± standard deviation. Student's t-tests performed for comparisons between the two groups.
groups, and the median postmenopausal time of the two groups lasted for about 9 years, as indicated in Table 1.

Similarly, the menopausal age of the cases in the MHT group did not differ from that in the non-MHT group \( (p > 0.05) \). As previously reported, most studies demonstrated that the menopause age was about 49 years \([26-28]\). Furthermore, nearly half of the interviewees in the medication group have been treated with hormone for 5–10 years, followed by 3–5 years \((29.6\%)\) and the rest for more than even 10 years. It is worth noting that the vast majority of these women were non-smokers in the two groups. On the contrary, some people had drinking habits. However, most of them were not accustomed to drinking, and there existed no statistical difference between the two groups. It was worth noting that the education level of the MHT group was relatively higher than that of the non-MHT group, considering that people with senior high school backgrounds or above accounted for up to 98.3%. On the contrary, the number of women in the control group with junior high school education or below was far more than that in the medication group \((24.4\% \text{ vs. } 1.7\%, \text{ respectively})\). Intriguingly, a significant difference in BMI between the medication group \((22.9 \text{ kg/m}^2)\) and the non-MHT group \((24.2 \text{ kg/m}^2)\) was also observed.

**Evaluation of the depression and anxiety levels of the interviewees**

Subsequently, we assessed these participants’ depression and anxiety status based on the CES-D and GAD-7 questionnaires. There were 20 items in the CES-D questionnaire, and each option was rated as \(0-3\). CES-D scores ranged from 0 to 60, with a cut-off value of 16 to indicate possible clinical depression. According to the overall scores, we found that 12.2% of the people in the non-MHT group were depressed; 5.2% of them were potentially depressed, while 4.3% of the medication group were depressed or likely to be depressed, respectively, as shown in Figure 1(A). The number of people with depression in the non-MHT group was much higher than that in the medication group. On the contrary, people without depression in the MHT group accounted for 91.3%, while in the control group this was 82.6% \( (p = 0.044) \). The content of the CES-D questionnaire included four factors: depressive emotion \((\text{questions 1, 3, 6, 9, 10, 14, 17 and 18})\), positive mood \((\text{questions 4, 8, 12 and 16})\), somatic symptoms or retarded activities \((\text{questions 2, 5, 7, 11, 13 and 20})\), and interpersonal relationship \((\text{questions 15 and 19})\). We further evaluated these four factors, and our data demonstrated that the differences in CES-D scores between the two groups fell chiefly into two aspects: depressive emotion, and somatic symptoms or retarded activities. The scores of these two aspects were relatively higher in the non-MHT group (Supplementary Figure 2).

Each item in the GAD-7 questionnaire was rated as \(0-3\). The total scores of 5, 10 and 15 represented the cut-off point of mild, moderate and severe anxiety, respectively. Unlike the results of the CES-D questionnaire, we did not observe any difference between the two groups in terms of the anxiety levels of these interviewees (Figure 1(B)). While over two-thirds of the population was in the first stage (non-anxious status), nearly one-fifth of the interviewed women were in a potentially mild anxious status. Besides, less than 5% of participants of the two groups were classified into moderate to severe anxiety levels.

To further confirm the underlying correlation between MHT intervention and mood disorders, GLM was adopted in this study to establish different regression models based on several variables, including age, education, BMI, age of

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**Figure 1.** Difference in anxiety and depression levels between the MHT and non-MHT groups. (A) CES-D score levels (no or potential depression and depression, respectively) between the MHT and non-MHT groups \( (p < 0.05) \). (B) GAD-7 score levels (minimal, mild, moderate or severe anxiety) between the MHT and non-MHT groups. CES-D, Center for Epidemiological Studies Depression Scale; GAD-7, Generalized Anxiety Disorder Screener; MHT, menopause hormone therapy.
menopause and postmenopausal time. As indicated in Supplementary Table 2, MHT served as a protective modulator in the depression status among these postmenopausal women, without or with adjusting for these potential confounding factors (81.0% vs. 91.3% not to be depressive for the controls and MHT-treated patients, respectively). Conversely, no significant differences were detected in the improvement of anxiety based on these three models. In general, the findings from GLM analysis were consistent with those from PSM evaluation. These results fully signified that MHT had more to do with the modulation of depression rather than anxiety.

Stratification analysis of BMI to reveal the effects of MHT on mood regulation

Obesity has been viewed as a risk factor for depression [29]. Given that BMI levels in the control group were far higher than those in MHT patients, we further detected differences in the CES-D and GAD-7 scores among people of different BMI levels. Our findings manifested that the average scores of CES-D in the overweight subgroup seemed higher than those in the other group but without significant difference (p = 0.295), as shown in Supplementary Figure 3(A). Furthermore, we focused independently on the stratified subgroups. We found that in the subgroup with BMI < 24 kg/m², the CES-D scores of the MHT and non-MHT groups did not vary significantly either (Supplementary Figure 3(B)). Interestingly, in the overweight subgroup, more than twice as many CES-D scores were determined in the non-MHT group than in the medication group with a statistical difference (p = 0.018), as presented in Supplementary Figure 3(C).

Likewise, we also carried out a stratification analysis of GAD-7 scores from the perspective of BMI subgroups. No difference was observed between the two subgroups with different BMI levels, as displayed in Supplementary Figure 4(A). At the same time, there appeared to be no significance regarding the difference in the GAD-7 scores between the medication and control groups in both of the BMI subgroups (Supplementary Figure 4(B) for non-overweight cases, Supplementary Figure 4(C) for cases with BMI ≥ 24 kg/m²).

Discussion

There are still limited studies to elucidate the underlying relationship between MHT, obesity and emotional problems. According to the STRAW +10 standard, the follicle stimulating hormone level will rise steadily, and estrogen remains low after women enter the +1C stage [17]. Therefore, we recruited people being postmenopausal for more than 3 years to explore the effects of MHT on regulating mood disorders.

During this particular period, people used to emphasize the effects of diseases induced by tissue degeneration while ignoring their emotional fluctuation [30]. Our results indicated that nearly one-fifth of women in the non-MHT group might have anxiety and depression. As previously reported, this proportion observably increased with age, and these non-treated patients recovered more slowly [31]. According to statistics, 15–25% of people over age 65 years were troubled by depressive symptoms, although most were not clinically diagnosed [32]. There were also about one-tenth of older people diagnosed with anxiety disorder [33]. Because of the specificity of the older population, more occult anxiety disorders have not been effectively identified [34]. Depressive symptoms may further aggravate cognitive impairment related to abnormal amygdala connections [35,36]. They will inevitably suffer from higher morbidity and mortality when confronted with medical diseases [37]. After further evaluation of the four factors in the CES-D questionnaire, we confirmed a correlation between somatic diseases and depression, consistent with the results of previous studies [38]. Anxiety was significantly correlated with all aspects of quality of life, which decreased with the aggravation of anxiety symptoms [39]. Globally, the number of people aged 60 years old or above will reach two billion by 2050 [40], and this signifies more attention to the mental health of older women.

MHT is a critical medical intervention in the health management of postmenopausal women. Emotional disorders tend to occur during the period of sex hormone fluctuations. However, there are also different points of view that menopause will not directly lead to emotional problems and that neurotransmitters cause emotional disorders [3]. Existed studies have been mainly devoted to exploring the emotional disorders during menopausal transition or early menopausal stages and the role of MHT in improving emotional disorders. At present, most studies have confirmed that MHT could improve mood disorders in the perimenopausal period [11,14]. Amygdala, hippocampal and several non-mesial temporal structures are the central areas involved in emotional regulation [3]. Estrogen therapy could protect the aforementioned structural changes during menopausal and postmenopausal periods and improve depression [41]. Estrogen receptor (ER) subtypes mainly consist of ERα and ERβ. Different subtypes of receptors have various actions on anxiety. ERα has an anxiety effect, while ERβ has a universal anti-anxiety impact [2,42]. We also found that long-term use of MHT could improve the emotional problems of postmenopausal women. For depression, there was a significant difference in CES-D scores between the two groups. In terms of anxiety status, no significant difference between the two groups was detected. Plasma estrogen levels were reported to be significantly lower in depressed women, suggesting that low estrogen could potentially lead to mood disorders or related symptoms [43].

Here, the demographics of the two groups were similar, but we found an interesting phenomenon in the baseline information that a significant difference in BMI between the two groups was determined. Body image is an essential related factor of menopausal depression and anxiety [44]. Estrogen plays a role through signal transduction of the ERα receptor. This receptor engages in promoting, on adipocytes, the ability of fat oxidation in women. Experiments have shown that estrogen is indispensable for the regulation of white fat. The amount of white adipose tissue will augment
after menopause and decline after MHT treatment [45]. ER knockout studies have indicated that ablation of ERα would increase white tissue and reduce energy consumption, while estrogen replacement would facilitate energy consumption and reduce the incidence of obesity [46]. A national survey found that women were 1.5–3 times more likely to suffer from severe depression than men, and obese women were more easily bothered by depression [47,48]. A similar observation was noticed in postmenopausal obese mice; they exhibited symptoms of anxiety and depression, alleviated after estrogen supplementation [49]. In our study, no significant differences in anxiety and depression scores were confirmed among postmenopausal women, whether overweight or normal. However, we found a significant difference in the CES-D score between the medication and non-MHT groups in overweight people, which demonstrated that MHT mainly improved the depression status of overweight patients, but not the anxiety condition, implicating that MHT might serve as an effective regulator for depression, and it is necessary to find other reliable ways to relieve anxiety among postmenopausal women.

Here, a series of comprehensive analyses have been performed based on PSM and stratification analysis by BMI to confirm the effects of MHT on mood disorders among postmenopausal women. The role of MHT was further determined by GLM analysis. As far as we know, the population in the medication group recruited has been arranged for MHT for a very long time in mainland China. However, it is necessary to emphasize the limitations of this study. It is critical to recruit more patients to improve the quality and reliability of the study. Besides, it really makes much sense to conduct a multicenter prospective cohort study to investigate the underlying causal relationship between MHT and mood disorders.

Conclusions

In the present study, postmenopausal women, especially the overweight women, who received MHT for more than 3 years exhibited an improved depressive status but not the anxiety feeling.

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Potential conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this article.

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