Clinical observation of menopause hormone therapy in euthyroid and mild subclinical hypothyroidism postmenopausal women

Wenxian Xu
Women's Hospital, School of Medicine, Zhejiang University
Yizhou Huang
Women's Hospital, School of Medicine, Zhejiang University
Linjuan Ma
Women's Hospital, School of Medicine, Zhejiang University
Peiqiong Chen
Women's Hospital, School of Medicine, Zhejiang University
Saisai Li
Women's Hospital, School of Medicine, Zhejiang University
Ketan Chu
Women's Hospital, School of Medicine, Zhejiang University
Yibing Lan
Women's Hospital, School of Medicine, Zhejiang University
Chunming Li
Women's Hospital, School of Medicine, Zhejiang University
Yang Song
Women's Hospital, School of Medicine, Zhejiang University
Qian Ying
Zhejiang Cancer Hospital
Jianhong Zhou (zhoujh1117@zju.edu.cn)
Women's Hospital, School of Medicine, Zhejiang University

Research Article

Keywords: Menopause hormone therapy, Postmenopausal women, Thyroid stimulating hormone, Mild subclinical hypothyroidism, Glucose and lipid metabolism

Posted Date: June 1st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1679966/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at BMC Endocrine Disorders on January 23rd, 2023. See the published version at https://doi.org/10.1186/s12902-023-01269-7.

Abstract

Objective:

To evaluate the endocrine hormone and metabolic indexes in euthyroid and mild subclinical hypothyroidism postmenopausal women after menopause hormone therapy (MHT).

Methods:

A retrospective study was conducted including 587 postmenopausal women received MHT, whose median (25-75th percentile) age was 52.00 (49.00–54.00) years. According to the state of thyroid stimulating hormone (TSH) level at the initial diagnosis, the patients were divided into three groups: I (euthyroid with low normal TSH range, *n* = 460), II (euthyroid with upper normal TSH range, *n* = 106) and III (mild subclinical hypothyroidism, *n* = 21). After continuous oral MHT regimen used same potency of estradiol for 6–18 month cycles, serum endocrine hormone and metabolic indexes were reassessed.

Results:

Compared with baseline, serum TSH level in group I and II changed with significant difference, but all values were within the normal range, no significant difference was found of serum TSH level in group III. After treatment, all serum free triiodothyronine and free thyroxine levels were within the normal range. Serum total cholesterol, triglyceride, fasting plasma glucose, fasting insulin levels and homeostasis model assessment of insulin resistance index were decreased in group I with significant differences. All lipid and glucose parameters were found no significant differences in group III before and after treatment.

Conclusions:

MHT did not affect thyroid function in euthyroid and mild subclinical hypothyroidism women. MHT led to an improvement of lipid and glucose indicators in euthyroid women with low normal TSH range.

Introduction

Menopause is characterized by the permanent cessation of menstrual periods as a result of a gradual irreversible loss of ovarian function. The decline in ovarian function, metabolic changes and co-morbidities cause a wide spectrum of symptoms[1]. Menopause hormone therapy (MHT) has been extensive studies proved to relieve climacteric symptoms, in addition, which is also the necessary medical measures for reducing the risk and mortality of cardiovascular diseases, preventing urogenital tract atrophy and osteoporosis[2].

Thyroid function and the gonadal axes are related throughout the woman's fertile period. The relationship between the two glands is mutual[3][4]. Thyroid hormone increase the synthesis of sex hormone binding globulin (SHBG), testosterone and androstenedione, reduce the clearance of estradiol and androgens and increase the conversion of androgens to estrone[5]. The main role of estrogens in thyroid physiology is related to the increase of the serum concentrations of thyroxine binding globulin (TBG)[6]. The fundamental essence of MHT is estradiol. It is important to note the effects of estrogens on thyroid function. The oral administration of estrogens causes a dose-dependent increase of the serum levels of TBG synthesized in the liver[7]. Previous study reported that oral MHT produced a marked increase in TBG levels and in total thyroxine (tT4), the average serum thyroid stimulating hormone (TSH) increased in postmenopausal women with primary hypothyroidism, in 40% of these women, the levothyroxine (L-T4) requirement increased[8]. Many epidemiological surveys reported the prevalence of subclinical hypothyroidism was higher compared to overt hypothyroidism in elderly women[9, 10]. It is not uncommon in postmenopausal women who seeking MHT combined with subclinical hypothyroidism. Up to now, few study assess the effects of MHT on thyroid function with subclinical hypothyroidism postmenopausal women, whether the use of MHT can lead to an increasing risk of hypothyroidism or an increasing demand for thyroxine has not been reported yet.

Previous studies proved that postmenopausal patients with hypothyroidism or subclinical hypothyroidism have adverse effects on lipid metabolism and the development of cardiovascular diseases[11]. Nevertheless, for postmenopausal women with thyroid dysfunction, whether the use MHT can also show favorable effects on lipid and glucose regulation remains unclear.

This study aims to assess the endocrine hormone and metabolic status in euthyroid and mild subclinical hypothyroidism postmenopausal women before and after MHT.

Methods

Study design and participants

Database was set up for patients underwent MHT during January 2010 to December 2020 on menopause clinic in Women's Hospital, Zhejiang University, School of Medicine. Baseline information, medical regimen, and follow-up records were collected and preserved in computer software. A total of 3108 MHT files had been established, from which we selected 587 postmenopausal women, aged 40–60 years cessation of menses over 12 months, a serum FSH level over 40 IU/L and within the normal range of fT3 and fT4, $0.3 \leq TSH < 10$ mIU/L at first visit, continuous received oral MHT regimen using same potency of estradiol for 6–18 month cycles. Participants were excluded if they reported: (i) a history of using estrogen and progestogen in latest three months at the first visit, (ii) a history of malignancies, (iii) unnatural menopause as a result of surgery, radiation or chemotherapy, (iv) diagnosis of any severe systematic or major organ diseases, (v) required treatment for thyroid dysfunction or a history of medication used to treat thyroid dysfunction, (vi) a history of psychological disorders and psychiatric,

(vii) a history of autoimmune disorders, (viii) a missing or incomplete blood results at follow-up, (ix) poor medication compliance.

The participants within the normal range of free triiodothyronine (fT3) and fT4 were divided into three groups according to the TSH values at the time of initial diagnosis: group I (euthyroid with low normal TSH range, $0.3 \leq TSH \leq 2.5$ mIU/L, $n = 460$), group II (euthyroid with upper normal TSH range, $2.5 < TSH \leq 4.5$ mIU/L, n = 106) and group III (mild subclinical hypothyroidism, $4.5 < TSH < 10$ mIU/L, n = 21). The grouping for TSH levels plan to further stratified the differences in metabolic indicators under different TSH levels in normal range referred to previous researches)[12–15]. The local ethical committee approved this study and an informed consent was obtained from each subject.

Assessment and laboratory analyses

Age, time of amenorrhea, age of menarche, height, weight, blood pressure, circumferences of waist and hip were recorded at first visit. All women provided peripheral blood to measure thyroid hormone, reproductive endocrine hormones, lipid and glucose metabolism parameters before and after MHT. Before blood sampling, participants were fasted for at least 8 h. The indexes evaluated in this paper included serum levels of TSH, fT3, fT4, estradiol (E_2), luteinizing hormone (LH), FSH, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), fasting insulin (FINS). In addition, homeostasis model assessment of insulin resistance (HOMA-IR) was used to assess insulin resistance.

Serum TSH, fT3, fT4 and insulin levels were measured by chemiluminescent microparticle immunoassay (CMIA), using the associated commercially kids for Abbott Architect i2000 (Abbott Laboratories, Abbott Park, IL, USA), the intra- and inter-assay coefficients of variations (CVs) for TSH tests were less than 3% and 5%, respectively. Serum levels of FSH, LH and E2 were determined by chemiluminescent immunoassay with commercially available kits, using an automated Roche Modular Analytics E170 immunoassay system (Roche Diagnostics, Meylan, France). Serum levels of TG, TC, HDL-C, LDL-C were measured by standard enzymatic, serum glucose was determined by hexokinase method, using the associated commercially kids for Beckman Coulter Chemistry Analyzer AU5800 (Beckman Coulter, Inc., Brea California, USA).

Statistical methods

All statistical analyses were conducted by Statistics Package for Social Sciences 26.0 software (SPSS Inc., Chicago, IL, USA). Data are reported as medians (25th percentile, 75th percentiles) for continuous variables and numbers (frequencies) for categorical variables, respectively. The Shapiro-Wilk test was utilized to analyze the normal distribution of continuous variables. For normally distributed data, inter-group comparisons were determined using the one way ANOVA, and intra-group comparisons were evaluated by the paired-samples t test. For non-normal distributed data, Wilcoxon signed-rank test was performed to demonstrate significant differences within groups, and Kruskal-Wallis H test was chosen for comparison between independent groups. Additionally, categorical variables were compared by the Chi-square test or Fisher's exact test, as appropriate. Results with $p < 0.05$ were considered significant.

Results

The baseline characteristics of the participants

The present study ultimately included 587 postmenopausal women. The median (25-75th percentile) age of all participants was 52.00 (49.00–54.00) years. The median (25-75th percentile) menopause age of all participants was 48.00 (45.00–51.00) years. The baseline demographic characteristics of the women in the three groups were comparable. No significant differences were observed on age, age of amenorrhea, time since amenorrhea, age of menarche, residence, educational level, height, weight, body mass index (BMI) status, waist circumference, hip circumference, waist to hip ratio or blood pressure condition across three groups (Table 1).

Table 1
Characteristics of the participants at Baseline

Variable	Group I (n = 460)	Group II (n = 106)	Group III (n = 21)	H/χ^2	p value[a]
Age, y	52.00 (48.25, 54.00)	53.00 (49.75, 54.00)	53.00 (48.50, 55.00)	0.643	0.725
Age of menopause, y	48.00 (45.00, 51.00)	48.00 (45.00, 50.25)	49.00 (45.50, 52.00)	0.645	0.724
Time since amenorrhea, m	29.00 (17.00, 53.00)	32.50 (16.75, 64.25)	31.00 (18.00, 64.00)	1.597	0.450
Age of menarche, y	14.00 (14.00, 16.00)	14.00 (13.25, 15.00)	14.00 (13.00, 16.00)	3.199	0.202
Residence				3.070	0.523
Urban	381 (82.8)	89 (84.0)	15 (71.4)		
Suburb	50 (10.9)	11 (10.4)	3 (14.3)		
Rural	29 (6.3)	6 (5.7)	3 (14.3)		
Educational level				2.743	0.602
Less than or equal to middle school diploma or equivalent	144 (31.3)	29 (27.4)	6 (28.6)		
High school	172 (37.4)	35 (37.4)	8 (38.1)		
≥ College degree	144 (31.3)	42 (39.6)	7 (33.3)		
Height, m	1.60 (1.56, 1.63)	1.60 (1.58, 1.63)	1.61 (1.54, 1.64)	3.632	0.163
Weight, kg	56.00 (51.00, 60.00)	56.50 (53.00, 60.00)	58.00 (52.75, 61.13)	2.156	0.340
BMI, kg/m^2	21.95 (20.34, 23.50)	21.76 (20.67, 23.75)	22.47 (20.37, 23.88)	0.795	0.672
Underweight	28 (6.1)	5 (4.7)	2 (9.5)	2.105	0.894
Normal weight	338 (73.5)	78 (73.6)	14 (66.7)		
Overweight	81 (17.6)	21 (19.8)	5 (23.8)		
Obesity	13 (2.8)	2 (1.9)	0 (0)		

Data are expressed as numbers (frequencies) or medians (25th percentile, 75th percentiles) as appropriate. $p < 0.05$ was considered significant. aComparison between groups by Kruskal-Wallis H test for continuous variables or by χ2 test/Fisher's exact test for categorical variables.

Abbreviation: BMI body mass index; SBP systolic blood pressure; DBP diastolic blood pressure.

Variable	Group I (*n* = 460)	Group II (*n* = 106)	Group III (*n* = 21)	H/χ^2	*p* value[a]
Waist circumference, cm	76.00 (72.00, 82.00)	77.00 (72.00, 82.00)	78.50 (71.50, 85.50)	0.414	0.813
Hip circumference, cm	92.00 (89.00, 96.00)	93.00(89.00, 96.00)	95.00 (88.50, 98.50)	1.353	0.508
Waist to hip ratio	0.83 (0.79, 0.87)	0.82 (0.78, 0.86)	0.83 (0.79, 0.87)	0.246	0.884
Hypertension				2.450	0.231
No	441 (95.9)	98 (92.5)	20 (95.2)		
Yes	19 (4.1)	8 (7.5)	1 (4.8)		
SBP, mmHg	120.00 (110.00, 124.00)	115.50 (110.00, 120.50)	120.00 (111.00, 120.00)	1.475	0.478
DBP, mmHg	76.00 (70.00, 80.00)	78.00 (70.00, 80.00)	75.00(69.50, 80.75)	0.025	0.987
Data are expressed as numbers (frequencies) or medians (25th percentile, 75th percentiles) as appropriate. $p < 0.05$ was considered significant. aComparison between groups by Kruskal-Wallis H test for continuous variables or by χ2 test/Fisher's exact test for categorical variables.					
Abbreviation: BMI body mass index; SBP systolic blood pressure; DBP diastolic blood pressure.					

Endocrine indicators before and after MHT

For reproductive endocrine hormone indicators, no significant differences were observed in the baseline serum levels of FSH or LH between three groups, while baseline serum level of E_2 was shown a statistical difference, but all in a quite low level without clinical difference. The treatment of all postmenopausal women decreased the serum FSH level and increased the serum E_2 level significantly in three groups. The serum LH level was decreased statistically but not in group III (Table 2).

Table 2
Thyroid and reproductive endocrine hormone parameters in euthyroid and subclinical hypothyroidism postmenopausal women before and after MHT

Variable	Group I (*n* = 460)	Group II (*n* = 106)	Group III (*n* = 21)	*F/H*	*p* value[a]
TSH (mIU/L)					
Before MHT	1.46 (1.08, 1.88)	3.12 (2.73, 3.64)	5.14 (4.86, 6.09)	300.526	0.000
After MHT	1.75 (1.24, 2.21)	2.74 (2.29, 3.22)	5.17 (3.09, 6.19)	68.322	0.000
t/Z	5.050	2.559	0.847		
p value[b]	0.000	0.010	0.397		
fT3 (pmol/L)					
Before MHT	4.38 (3.96, 4.73)	4.45 (3.96, 4.87)	4.37 (4.13, 4.79)	1.276	0.528
After MHT	4.26 (3.91, 4.58)	4.19 (3.87, 4.66)	3.96 (3.47, 4.23)	2.683	0.070
t/Z	1.999	1.557	2.929		
p value[b]	0.047	0.119	0.013		
fT4 (pmol/L)					
Before MHT	13.82 (12.64, 15.04)	13.22 (12.38, 14.78)	13.33 (11.69, 14.74)	5.175	0.075
After MHT	13.36 (12.33, 14.58)	13.26 (12.32, 14.50)	12.83 (10.97, 14.13)	2.749	0.253
t/Z	3.181	1.153	0.853		
p value[b]	0.001	0.249	0.410		
LH(IU/L)					

Data are expressed as medians (25th percentile, 75th percentiles). $p < 0.05$ was considered significant. a*p* values are for between-group differences by Kruskal-Wallis H test/one way ANOVA. b*p* values are for within-group differences by Wilcoxon signed-rank test or paired-samples t test. c$p < 0.05$ and further between-group differences by post hoc test with Bonferroni correction as follows: I vs. II $Z = -26.895$, $p = 0.311$; I vs. III $Z = -72.162$ $p = 0.100$; II vs. III $Z = -99.057$, $p = 0.019$.

Abbreviation: MHT menopause hormone therapy, TSH thyroid stimulating hormone, fT3 free triiodothyronine, fT4 free thyroxine, LH luteinizing hormone, FSH follicle-stimulating hormone, E_2 estradiol.

Variable	Group I (n = 460)	Group II (n = 106)	Group III (n = 21)	F/H	p value[a]
Before MHT	36.42 (27.98, 46.59)	35.70 (27.98, 43.43)	40.27 (28.83, 43.54)	1.054	0.590
After MHT	31.75 (24.11, 42.51)	31.38 (22.57, 41.14)	29.71 (19.06, 38.40)	0.941	0.625
t/Z	6.157	2.252	1.614		
p value[b]	0.000	0.024	0.123		
FSH(IU/L)					
Before MHT	77.30 (63.89, 93.33)	75.08 (64.00, 90.96)	72.90 (54.75, 85.98)	2.341	0.310
After MHT	52.11 (39.51, 67.48)	51.61 (36.89, 67.47)	42.59 (34.16, 62.75)	2.002	0.368
t/Z	14.473	6.070	4.842		
p value[b]	0.000	0.000	0.000		
E_2 (pmol/L)					
Before MHT	18.35 (18.35, 33.97)	18.40 (18.35, 38.05)	18.35 (18.35, 18.52)	7.828	0.020[c]
After MHT	71.41 (18.40, 170.30)	87.43 (25.51, 212.15)	79.38 (22.40, 193.30)	2.677	0.262
t/Z	10.970	6.059	3.294		
p value[b]	0.000	0.000	0.001		

Data are expressed as medians (25th percentile, 75th percentiles). $p < 0.05$ was considered significant. ap values are for between-group differences by Kruskal-Wallis H test/one way ANOVA. bp values are for within-group differences by Wilcoxon signed-rank test or paired-samples t test. c$p < 0.05$ and further between-group differences by post hoc test with Bonferroni correction as follows: I vs. II Z = -26.895, p = 0.311; I vs. III Z = -72.162 p = 0.100; II vs. III Z = -99.057, p = 0.019.

Abbreviation: MHT menopause hormone therapy, TSH thyroid stimulating hormone, fT3 free triiodothyronine, fT4 free thyroxine, LH luteinizing hormone, FSH follicle-stimulating hormone, E_2 estradiol.

For thyroid hormone indicators, no significant differences were observed between three groups in serum fT3 or fT4 before and after treatment. At follow-up, all serum fT3 and fT4 levels were in a normal range. In group I, patients increased the serum TSH level, decreased the serum fT3 and fT4 levels significantly. In group II, patients decreased the serum TSH level significantly with no differences in serum fT3 or fT4

levels. The serum TSH levels between two euthyroid groups still in a normal range. In group III, patients decreased the serum fT3 level significantly with no difference in serum TSH or fT4 levels (Table 2).

Lipid and Glucose metabolism parameters before and after MHT

No statistically significant difference was observed between three groups with regard to baseline serum levels of TG, TC, HDL-C or LDL-C. At follow-up, postmenopausal women showed a marked decline in serum TG and TC levels significantly compared with baseline in group I and group II, while the serum levels of HDL-C or LDL-C had no significant changes. Moreover, no significant differences were noted in before-mentioned lipid parameters at follow-up and the changes from baseline in group III (Table 3).

Table 3
lipid and glucose metabolism parameters in euthyroid and subclinical hypothyroidism postmenopausal women before and after MHT

Variable	Group I (*n* = 460)	Group II (*n* = 106)	Group III (*n* = 21)	*F/H*	*p* value[a]
TG(mmol/L)					
Before MHT	1.07 (0.78, 1.51)	1.05 (0.87, 1.41)	0.84 (0.77, 1.90)	0.735	0.693
After MHT	1.00 (0.67, 1.36)	0.89 (0.75, 1.17)	1.02 (0.64, 1.44)	0.834	0.659
t/Z	2.860	2.657	0.632		
p value[b]	0.004	0.008	0.528		
TC(mmol/L)					
Before MHT	5.19 (4.61, 5.81)	5.27 (4.67, 5.84)	4.93 (4.32, 5.61)	1.484	0.476
After MHT	5.07 (4.44, 5.64)	4.76 (4.16, 5.35)	4.70 (4.18, 5.81)	5.332	0.070
t/Z	3.892	2.691	0.109		
p value[b]	0.000	0.007	0.913		
HDL-C(mmol/L)					
Before MHT	1.47 (1.26, 1.72)	1.44 (1.26, 1.72)	1.47 (1.15, 1.88)	0.141	0.932
After MHT	1.44 (1.25, 1.70)	1.46 (1.26, 1.58)	1.41 (1.24, 1.72)	0.150	0.928
t/Z	0.895	0.327	0.150		
p value[b]	0.371	0.745	0.883		
LDL-C(mmol/L)					
Before MHT	2.88 (2.44, 3.38)	2.91 (2.42, 3.62)	2.54 (1.94, 3.03)	4.685	0.096
After MHT	2.86 (2.41, 3.34)	2.59 (2.35, 3.15)	2.64 (2.16, 3.47)	4.034	0.133
t/Z	0.817	0.974	1.459		
p value[b]	0.414	0.330	0.145		
FPG (mmol/L)					

Data are expressed as medians (25th percentile, 75th percentiles). $p < 0.05$ was considered significant. a*p* values are for between-group differences by Kruskal-Wallis H test/one way ANOVA. b*p* values are for within-group differences by Wilcoxon signed-rank test or paired-samples t test.

Abbreviation: MHT menopause hormone therapy, TG triglyceride, TC total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C Low-density lipoprotein cholesterol, FPG fasting plasma glucose, FINS fasting insulin, HOMA-IR homeostasis model assessment of insulin resistance.

Variable	Group I ($n = 460$)	Group II ($n = 106$)	Group III ($n = 21$)	F/H	p value[a]
Before MHT	5.26 (4.97, 5.62)	5.26 (4.89, 5.56)	5.18 (4.93, 5.49)	1.175	0.556
After MHT	5.09 (4.85, 5.35)	5.12 (4.87, 5.36)	4.99 (4.57, 5.37)	1.669	0.434
t/Z	5.512	0.711	1.034		
p value[b]	0.000	0.477	0.301		
FINS (μU/ml)					
Before MHT	5.40 (4.10, 7.20)	5.60 (3.90, 8.00)	6.15 (3.70, 6.88)	0.086	0.958
After MHT	4.80 (3.60, 6.80)	5.10 (3.90, 6.90)	4.85 (3.85, 6.58)	0.874	0.646
t/Z	3.816	1.728	0.653		
p value[b]	0.000	0.084	0.513		
HOMA-IR					
Before MHT	1.33 (0.94, 1.77)	1.30 (0.88, 1.97)	1.38 (0.88, 1.60)	0.018	0.991
After MHT	1.08 (0.78, 1.55)	1.19 (0.86, 1.59)	1.13 (0.78, 1.52)	1.076	0.584
t/Z	4.442	1.806	0.992		
p value[b]	0.000	0.071	0.338		

Data are expressed as medians (25th percentile, 75th percentiles). $p < 0.05$ was considered significant. ap values are for between-group differences by Kruskal-Wallis H test/one way ANOVA. bp values are for within-group differences by Wilcoxon signed-rank test or paired-samples t test.

Abbreviation: MHT menopause hormone therapy, TG triglyceride, TC total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C Low-density lipoprotein cholesterol, FPG fasting plasma glucose, FINS fasting insulin, HOMA-IR homeostasis model assessment of insulin resistance.

No observable difference was demonstrated in terms of the baseline serum levels of FPG, FINS or HOMA-IR in three groups. As compared to baseline values, group I postmenopausal women exhibited a significant decline in serum levels of FPG and FINS, as well as HOMA-IR after MHT. In group II and III women, the serum concentrations of FPG, FINS and HOMA-IR were not affected significantly compared with baseline (Table 3).

Discussion

This retrospective study observed the clinical data in euthyroid and mild subclinical hypothyroidism postmenopausal women underwent MHT, compared endocrine hormone levels and metabolic status before and after MHT. In this study, there were no statistically significant differences in age, time of

menopause, BMI and other baseline indexes among the three groups before medication, all participants used oral MHT with same potency of estrogen, the medication regiments among the three groups were comparable.

It had been consensus that MHT through exogenous supplementation of estrogen to reduce the level of FSH in serum, and maintain a certain E_2 level to meet the needs of various organs in the body, so as to relieve menopausal symptoms[16]. In our study, the serum FSH decreased and E_2 increased in all three groups comparing with the baseline, and no difference at follow-up between the three groups were noted, that is consistent with previous researches.

Previous studies had examined the effects of MHT on thyroid function in euthyroid postmenopausal women. In the study of Benencia et al[17], postmenopausal women used oral MHT showed serum TBG and tT4 increased at 3, 6 and 12 months, but within the normal range, serum TSH, fT4 and total triiodothyronine (tT3) levels did not change significantly and remained within the normal range. Ceresini et al.[18] reported serum TSH did not change significantly after 1 year estrogen therapy in euthyroid postmenopausal women. Marqusee et al.[19] revealed the administration of conjugated estrogen for 6 weeks increased serum TSH concentrations, but does not alter fT4 index values in postmenopausal women, moreover, serum TSH values remained within the normal range. For postmenopausal women with thyroid dysfunction, only a little study observed the effects caused by MHT. In a 48-week study, Arafah investigated the effects of oral MHT on thyroid function in postmenopausal women, in women with normal thyroid function, TBG and tT4 levels increased, fT4 and TSH levels did not change, in women with primary hypothyroidism in the meantime received L-T4 therapy, oral MHT produced a marked and sustained increase in TBG levels and a parallel increase in tT4 levels, however, in contrast to euthyroid women, the serum fT4 levels decreased significantly and the average serum TSH levels increased markedly, 40% patients had their L-T4 doses increased after their TSH levels had exceeded the predetermined limits set in the protocol [8, 20]. Our study found that after MHT, serum TSH increased and fT3, fT4 decreased in euthyroid women with a lower normal TSH level, serum TSH decreased and fT3, fT4 remained no change in euthyroid women with a upper normal TSH level, but all serum TSH, fT3 and fT4 levels were still within the normal range of reference values, this result is consistent with previous researches. In mild subclinical hypothyroidism postmenopausal women, serum fT3 level decreased significantly, while still within the normal range, serum TSH and fT4 showed no significant change before and after treatment. This study is the first one analyzed the effects of MHT on mild subclinical hypothyroidism postmenopausal women. The result suggested that MHT has no significant effect on thyroid function, does not lead to increased demand for thyroxine or aggravate the trend of clinical hypothyroidism for mild subclinical hypothyroidism postmenopausal women.

Consistent results from several large randomized controlled trials indicated that MHT produced significant increasing in HDL-C,TG levels, and reductions in LDL-C levels, also led to a decline in FPG levels and decreased the incidence of type 2 diabetes[21–24]. This study showed that MHT led to improvements of lipid parameters in euthyroid postmenopausal women, which is consistent with previous studies in portion of lipid indicators, while there was no significant changes of lipid parameters

in mild subclinical hypothyroidism postmenopausal women before and after treatment. Possibly elevated TSH impairs the ability of MHT to improve lipid levels, further research is required. In this study, we found that MHT significantly decreased FPG, FINS and HOMA-IR in euthyroid postmenopausal women with low normal TSH range. However, there were no significant differences in between euthyroid women with upper normal TSH level or mild subclinical hypothyroidism women. Based on the present results, women with low normal TSH range showed more obvious within-group improvements in glucose and lipid metabolism after MHT.

There are several potential limitations to this study. First, the investigation was a retrospective analysis. Second, the sample size of women in group III was too small. Third, selection and recall bias existed in the recruitment of the participants. Given these limitations, further prospective studies with larger sample sizes and homogeneous hormone therapies are required.

Conclusions

MHT can effectively regulate reproductive hormone levels and does not affect thyroid function in euthyroid and mild subclinical hypothyroidism postmenopausal women. MHT led to significant improvements of lipid and glucose levels in euthyroid postmenopausal women with low normal TSH range, while no significant different were found of lipid or glucose indicators in mild subclinical hypothyroidism postmenopausal women.

Declarations

Ethical Statement and consent to participate

Ethical approval was obtained from the Ethics Committee of Women's Hospital, Zhejiang University, School of Medicine. All the methods were performed in accordance with the relevant guidelines and regulations. All participating women provided their written informed consent for this study.

Consent to publish

Not applicable.

Funding

This work was supported by grants from National Natural Science Foundation of China [grant number 81873810, 82001463 and 82003469].

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgements

The authors thank all women who took the time to participate in this study.

Authors' contributions

JZ conceived and designed the research. WX, YH, PC, and SL performed the experiments. WX, YH, and QY conducted statistical analyses. WX and YH wrote the manuscript. LM, KC, YL, CL, and YS revised the manuscript. All the authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Baber RJ, Panay N, Fenton A. 2016 IMS Recommendations on womens midlife health and menopause hormone therapy. Climacteric. 2016;19(2):109–150.
2. Flores VA, Pal L, Manson JE. Hormone Therapy in Menopause: Concepts, Controversies, and Approach to Treatment. Endocr Rev. 2021;42(6):720–752.
3. del Ghianda S, Tonacchera M, Vitti P. Thyroid and menopause. Climacteric. 2014;17(3):225–234.
4. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010;31(5):702–755.
5. Torre F, Calogero AE, Condorelli RA, et al. Effects of oral contraceptives on thyroid function and vice versa. J Endocrinol Invest. 2020;43(9):1181–1188.
6. Ain KB, Mori Y, Refetoff S. Reduced Clearance Rate of Thyroxine-Binding Globulin (TBG) with Increased Sialylation: A Mechanism for Estrogen-Induced Elevation of Serum TBG Concentration. J Clin Endocrinol Metab. 1987:65(4):689–696.
7. Bhavnani BR, Nisker JA, Martin J, et al. Comparison of Pharmacokinetics of a Conjugated Equine Estrogen Preparation (Premarin) and a Synthetic Mixture of Estrogens (C.E.S.) in Postmenopausal Women. J Soc Gynecol Investig. 2000;7(3):175–183.
8. Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. N Engl J Med. 2001;344(23):1743–1749.
9. Uygur MM, Yoldemir T, Yavuz DG. Thyroid disease in the perimenopause and postmenopause period. Climacteric. 2018;21(6):542–548.
10. Kim Y, Chang Y, Cho IY, et al. Menopausal stages and prevalence of thyroid dysfunction. Thyroid. 2022; online ahead of print. doi: 10.1089/thy.2021.0544.
11. Dalal D, Dahiya K, Malhotra V, et al. A comparison of reproductive hormones and biochemical parameters in hypothyroid and euthyroid postmenopausal women. Clin Lab. 2020;66(10):2087–2090.

12. Ruhla S, Weickert MO, Arafat AM, et al. A high normal TSH is associated with the metabolic syndrome. Clin Endocrinol. 2010;72(5):696–701.
13. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005;90(9):5483–5488.
14. Petrosyan L. Relationship between high normal TSH levels and metabolic syndrome components in type 2 diabetic subjects with euthyroidism. Journal of Clinical and Translational Endocrinology. 2015;2(3):110–113.
15. Kratzsch J, Fiedler GM, Leichtle A, et al. New reference intervals for thyrotropin and thyroid hormones based on national academy of clinical biochemistry criteria and regular ultrasonography of the thyroid. Clin Chem. 2005;51(8):1480–1486.
16. Ushiroyama T, Sakai M, Higashiyama T, et al. Estrogen replacement therapy in postmenopausal women: a study of the efficacy of estriol and changes in plasma gonadotropin levels. Gynecol Endocrinol. 2001;15(1):74–80.
17. Benencia H, Ropelato MG, Rosales M, et al. Thyroid profile modifications during oral hormone replacement therapy in postmenopausal women. Gynecol Endocrinol. 1998;12(3):179–184.
18. Ceresini G, Milli B, Morganti S, et al. Effect of estrogen therapy for 1 year on thyroid volume and thyroid nodules in postmenopausal women. Menopause. 2008;15(2):326–331.
19. Marqusee E, Braverman LE, Lawrence JE, et al. The Effect of Droloxifene and Estrogen on Thyroid Function in Postmenopausal Women. J Clin Endocrinol Metab. 2000;85(11):4407–4410.
20. Mazer NA. Interaction of Estrogen Therapy and Thyroid Hormone Replacement in Postmenopausal Women. Thyroid. 2004;14(Suppl 1):S27-34.
21. Castelo-Branco C, Blümel JE, Roncagliolo ME, et al. Age, menopause and hormone replacement therapy influences on cardiovascular risk factors in a cohort of middle-aged Chilean women. Maturitas. 2003;45(3):205–212.
22. Hulley S, Grady D, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA. 1998;280(7):605–613.
23. Mauvais-Jarvis F, Manson JAE, Stevenson JC, et al. Menopausal hormone therapy and type 2 diabetes prevention: Evidence, mechanisms, and clinical implications. Endocr Rev. 2017;38(3):173–188.
24. Margolis KL, Bonds DE, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia. 2004;47(7):1175–1187.