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ORIGINAL ARTICLE

Association between hormone therapy and weight gain in the menopause transition and after menopause: a systematic review and meta-analysis

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Abstract

Objectives: to conduct a systematic review and meta-analysis in order to assess whether hormone therapy (HT) increases weight in women in the menopausal transition and after menopause.

Method: this article proposes an update to the systematic review published in 2005 by the Cochrane Library (Kongnyuy EJ et al 2005) with reference to studies assessing weight changes in women receiving HT from 1986 to 2005. Following PRISMA recommendations, we included randomized controlled trials (RCTs)) from May 2005 onwards from Medline, Embase, and the Cochrane CENTRAL databases. Standardized mean differences (SMD) and 95% confidence intervals (CI) were calculated. Two authors independently assessed the risk of biases in the selected studies.

Results: ten RCTs were included, totaling 2,588 HT users and 764 non-users. Different regimens, dosages, and routes of administration in HT users were analyzed and compared to non-users. The results did not show statistically significant differences for most of the HT regimens evaluated. There was significant weight gain only in patients using EEC alone at dosages of 0.45 mg/day and 0.3 mg/day when compared to placebo (p 0.01); as well as in patients receiving esto-progestative combinations of 0.5 mg/day 17-beta-estradiol (E2) + 100 mg/day progesterone, with a 0.7 kg weight increase (p 0.032). On the other hand, the combinations of 1 mg/day estradiol valerate + 3 mg/day drospirenone showed a -1.0 kg reduction (p = 0.04), whereas a -0.2 kg reduction (p = 0.001) was identified in patients using 1 mg / day estradiol (E) + 0.5 mg norethisterone acetate (NETA). Tibolone therapy showed no statistically significant changes in weight. After performing a meta-analysis, the comparative results between users and non-users showed that there was a slight weight increase (+0.279 kg ; CI -1.71 to 2.27) in patients using 0.625 mg/day conjugated equine estrogen (CEE) + 2.5 mg/day medroxyprogesterone acetate (MPA). As for the patients receiving 2.5 mg/day Tibolone, weight gain (+0.670 kg; CI from -1.14 to 2.48) was also observed in them. However, these increases were not significant when compared to non-HT users.

Conclusions: most regimens studied showed that patients using HT in the menopausal transition and after menopause did not show significant weight gain. The only combination that showed weight gain was 0.5 mg/day 17-beta-estradiol (E2) + 100 mg/day progesterone observed, while there was weight reduction in patients using 1 mg/day estradiol valerate + 3 mg/day drospirenone and 1 mg/day estradiol (E) + norethisterone acetate.

Keywords: postmenopause; menopause; climacteric; hormone replacement therapy; body mass index; body weight

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Authors summary

Why was this study done?
This article is an update of the systematic review published in 2005 by the Cochrane Library (Kongnyuy EJ et al 2005) on the effects of hormone therapy on weight gain in women in the menopausal transition and after menopause. Therefore, as this is an important topic for the medical community and society, we carried out this systematic review to clarify the beliefs and insecurities that are one of the main causes of low adherence and abandonment of treatment with hormone therapy.

What did the researchers do and find?
A systematic review and meta-analysis was performed, with the aim of synthesizing available data from relevant randomized controlled trials and exploring associations between hormone therapy and weight gain in climacteric women. In most of the articles included, no significant weight gain was observed, either with the isolated use of estrogen (E) in different schemes, dosages and routes of administration, or in those who received E + P combined therapy, when compared to non-users. However, some formulations show significant changes in the weight of HT users: weight gain with 0.5 mg/day of 17-beta-estradiol (E2) + 100 mg/day of progesterone versus weight reduction with 1 mg of estradiol valerate /day + drospirenone 3 mg/day and estradiol (E) 1 mg/day + norethisterone acetate.

What do these findings mean?
It is essential that the medical community becomes aware that most TH formulations do not show significant weight changes, so that physicians can prescribe TH based on the evidence published in the literature.

Highlights
• This is a systematic review and meta-analysis in order to assess whether hormone therapy (HT) increases weight in women in the menopausal transition and after menopause.
• Different regimens, dosages, and routes of administration in HT users were analyzed and compared to non-users.
• Most regimens studied showed that patients using HT in the menopausal transition and after menopause did not show significant weight gain.

INTRODUCTION

The stages of the menopausal transition and after menopause are characterized by a progressive reduction in ovarian steroid production. Clinically, women may have hot flashes, insomnia, genitourinary syndrome, changes in body fat distribution, as well as they can be at a greater risk of suffering from diseases such as cardiovascular disease and osteoporosis[1-5].

Hormone therapy (HT) is prescribed especially to alleviate hot flashes and genitourinary syndrome symptoms. However, many women report they fear to use HT as they believe it is the cause of breast cancer and weight gain, which explains the low adherence to treatment[6-9].

Nevertheless, it must be considered that regardless of whether HT is used or not, there already exists a physiological tendency for weight gain at such transitional and postmenopausal stages[10,11].

Hence physicians and female patients still express their doubts as to whether HT can lead to weight gain. Therefore, in an attempt to address and clarify these questions, two systematic reviews were carried out: one by Kongnyuy *et al.,* (1999) and another by Higgins & Green (2005), who reached the conclusion that HT does not promote weight gain[12, 13].

Now, with the development of new HT regimens and 18 years having elapsed since the latest systematic review, the topic HT/weight gain still deserves to be discussed due to doubts and insecurities, which persists not only among female patients, but also among physicians.

This systematic review aims to solve the doubts still existing on the matter.

METHODS

Study Design

This systematic review was carried out based on a protocol for selecting articles called PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), which includes the eligibility criteria and methodology used (14) and which can be accessed by using the PROSPERO ID number : CRD42022240772[15].

Study Location and Period

The search was restricted to articles published from January 2004, which the date of the latest article included in the latest systematic review relevant to the matter, which was published by Kongnyuy et al, 2005[12].

Study Population and Eligibility Criteria

Only controlled trials (RCTs) that equate body weight or BMI of patients in the randomized menopausal transition or after menopause who were hormone therapy (HT) users. As HT, combinations of estrogen and progesterone, estrogen alone or tibolone were considered.

Data collection

In this review, PubMed (MEDLINE), LILACS, SCIELO, EMBASE and the Cochrane Central Register of Randomized Controlled Trials/CENTRAL databases were consulted. The selected articles were published in English, Spanish, and Portuguese.

Data Analysis

The search strategy followed the one standardized in the latest systematic review published by the Cochrane Library (Kongnyuy et al, 2005). The period we searched was May 2005 – February 2023 and the keywords used in the query were the following:

(Postmenopause OR postmenopausal OR menopause OR menopausal OR post menopause$ OR perimenopause OR peri menopause$ OR climacteric$) AND (estrogens OR Hormone Replacement Therapy OR Estrogen Replacement Therapy OR Estradiol OR HRT OR

hormone therapy OR hormone replacement OR estrogen therapy OR estrogen replacement OR Progesterone OR progestogen$ OR Progestins) AND (obese OR Obesity OR Body Mass Index OR Body Weight OR BMI OR Body Composition OR Skinfold Thickness OR Body Constitution OR body fat OR Adipose Tissue OR fat mass OR adiposity OR waist - hip ratio OR Anthropometry) .

Articles were selected following careful analysis of titles and abstracts in order to predict the relevance of the full text. After this step, all articles were read in full and independently by two raters.

Data from the selected articles were stored in a customized table containing the following variables: author's name, year the study was published, patient follow-up time, description of the evaluated HT and weight control (kg) before the use of HT or control (non-HT users), and weight gain or loss after HT use or control (non-HT users), accompanied by means and standard deviations (Table 2).

Risk of biases in each study

The quality of the included studies was evaluated independently by two reviewers, based on criteria previously defined by a scale for assessing the risk of biases.

The scale used in the present review was the JADAD scale, which analyzes the risk of biases as rated from 0 to 5 following an assessment of the analysis of variables such as randomization adequacy, allocation, double blinding, and withdrawals and dropouts[16]. Articles scored below 3 (poor methodological quality and high risk of biases) were excluded from the present review.

Summarization measures

Continuous variables were extracted and expressed as means, standard deviations, and differences in means, using a statistical significance level of 5%.

Summary of results

The meta-analysis was performed by using the Excel software; in the cases of true heterogeneity (ie, without publication biases), random-effect analysis was employed. Heterogeneity was measured by I2, being considered relevant when it was ≥ 50%.

Continuous variables were expressed as means and standard deviations, with a statistical significance of 5%.

Since this is an analysis with quantitative variables, it was not possible to draw a forest plot for the meta-analysis presented above. If qualitative variables had been evaluated instead, a specific graph could then be displayed.

Risk of biases across studies

For those cases involving more than one study with the same aggregate design, the risks of global biases were considered to be the same as those in the individual assessment.

RESULTS

Selection of articles

A total of 5,930 articles were retrieved and, after excluding those that did not meet the selection criteria, 15 studies were identified (Figure 1).

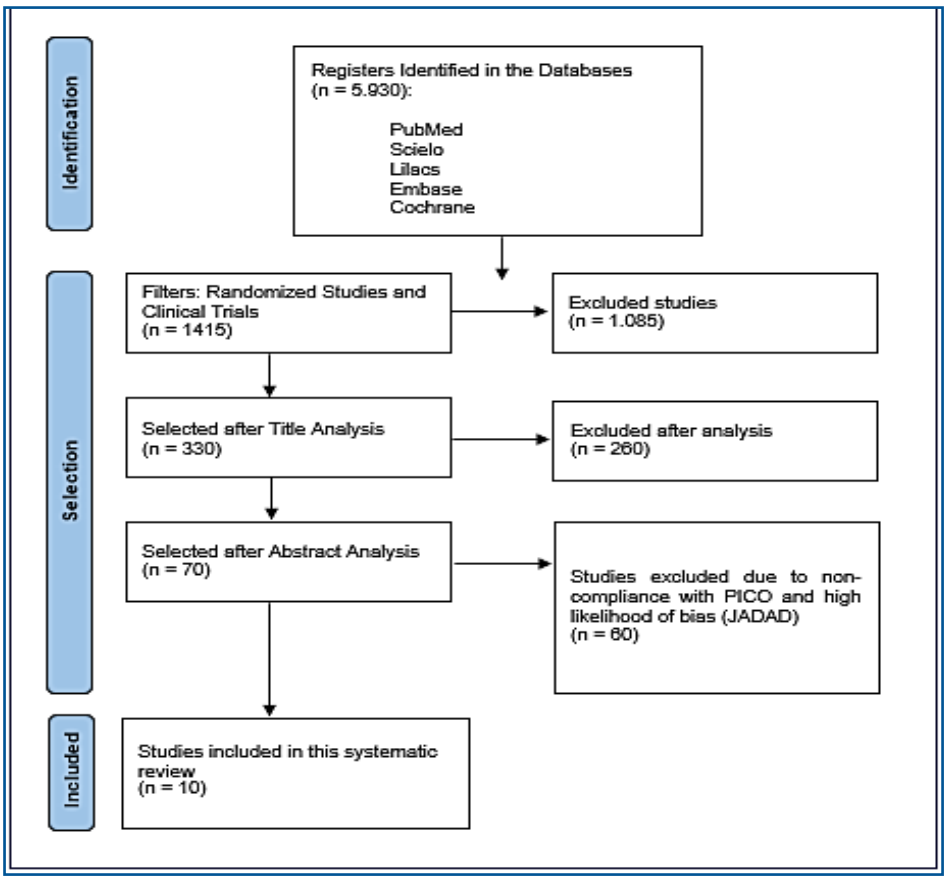

Figure 1: Article selection flowchart.

Characteristics of the studies

The number of evaluated women totaled 3,954, with 2,945 HT users and 1,009 controls/placebo. The mean follow-up period was 11.68 months, with a range of 2-36 months.

Biases

The 15 articles were assessed for bias according to the JADAD scale[16] (Figure 2). Thus, after assessing biases, 5 articles were excluded, leaving 10 studies with 3,352 women (2,588 HT-users and 764 non-users/placebo).

Table 1: Jadad scale for assessing the risk of bias in randomized clinical trials.

Study	Authors	Jadad scale
1	Yasui et al.[17]	1
2	Chen et al.[18]	3
3	Sites et al.[19]	3
4	Tugrul et al.[20]	1
5	Odabasi et al.[21]	3
6	Yüksel et al.[22]	3
7	Tommaselli et al.[23]	3
8	Zang et al.[24]	1
9	Thorneycroft et al.[25]	3
10	Yüksel et al.[26]	1
11	Dedeoglu et al.[27]	2
12	Ziaei et al.[28]	3
13	Paoletti et al.[29]	5
14	Deng et al.[30]	3
15	Black et al.[31]	4

Study results

The results of the 10 articles included are described below (Table 1).

Hormone therapy with estrogens/ progesterones

a.Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA)

Chen *et al.* compared women after menopause 0.625 mg/day CEE+ 2.5 mg/day MPA with placebo users/ non-HT users over a 36-month period. The mean age of HT users was 62.9 ± 7.2, whereas in the control group, it was 63.4 ± 7.2. Both groups showed weight gain, with no statistical significance (p = 0.32)[18].

Sites et al. compared two groups of women in the perimenopause or at the initial stage after menopause: one group receiving 0.625 mg/day CEE + 2.5 mg/day MPA with a mean age of 50.9 ± 3.7 and another group of non-users (control) with a mean age of 51.6 ± 3.6, at a 24-month follow-up. They observed a +0.30 kg (SD ± 0.2) weight gain in HT users and +0.50 kg (SD ± 0.7) in the control group, with no significant difference (p = 0.79) between them[19].

Thorneycroft *et al.* followed up eight groups for 24 months: seven groups of HT users, with formulations containing different dosages of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) and one group of non-users/placebo (n = 94). The groups/results were: I. 0.625 mg/day CEE alone (n = 97) exhibited a +1.88 kg weight gain (SD ± 0.92); II. 0.625 mg/day CEE + 2.5 mg/day MPA (n = 86) showed a weight gain of +1.14 kg (SD ± 0.66); III. 0.45 mg/day CEE alone (n = 95) revealed a weight gain of +0.32 kg (SD ± 0.57); IV. 0.45 mg/day CEE + 2.5 mg/day MPA (n = 96) showed a weight gain of +1.82 kg (SD ± 0.5); V. 0.45 mg/day CEE + 1.5 mg/day MPA (n = 94) showed a weight gain of +1.42 kg (SD ± 0.41); VI. 0.3 mg/day CEE alone (n = 89) revealed a weight gain of +0.23 kg (SD ± 0.4); VII. 0.3 mg/day CEE + 1.5 mg/day MPA (n = 98) showed an increase in weight of +1.29 kg (SD ± 0.47); VIII. Placebo showed a weight gain of +2.63 kg (SD ± 0.58). Patients using CEE at dosages of 0.45 mg/day and 0.3 mg/day showed significant, less weight gain when compared to placebo (p 0.01); the other HT groups did not differ from non-users (p > 0.05)[25].

In our search, only the study by Thorneycroft et al. evaluated the use of estrogens alone, namely in their groups I and VI, as already described.

b.Conjugated equine estrogen (CEE) + micronized progesterone or dydrogesterone

Deng et al. analyzed three groups of women after menopause for 12 months:

1. users of CEE at 0.625 mg/day + and micronized progesterone at 100 mg/day (mean age 51.7 ± 3.1) who had a weight loss of -0.1 kg (SD ± 3.0);

2. users of CEE at 0.3 mg/day + micronized progesterone at 100 mg/day (mean age 52.1 ± 3.9) who had a weight increase of +0.1 kg (SD ± 2.0);

3. users of CEE at 0.625 mg/day + dydrogesterone at 10 mg/day (mean age 52.0 ± 4.1) who showed a weight loss of -0.6 kg (SD ± 2.6).

The analysis across groups did not show any significant differences (p > 0.05)[30].

c. 17-beta-estradiol (E2) + progesterone

Black *et al.* evaluated users of 17-beta-estradiol (E2) + progesterone at different dosages after a 12-month period. Group I used 1 mg/day E2 + 100 mg/day progesterone (n = 282), with a weight gain of +0.3 kg (SD ± 4.4); group II received 0.5 mg/day E2 + 100 mg/day progesterone (n = 305) and showed a weight gain of +0.7 kg (SD ± 4.4); group III, with 0.5 mg/day E2 + 50 mg/day progesterone (n = 312), showed a weight gain of +0.5 kg (SD ± 4.3); group IV was given 0.25 mg/day E2 + 50 mg/ day progesterone (n = 280) and exhibited a weight gain of +0.3 kg (SD ± 4.2). All of them were then compared to non-users/control (n = 93), and the results showed that the final weight loss was -0.3 kg (SD ± 4.3). Groups I, III, and IV did not show statistically significant differences (p 0.249; p 0.133; p 0.113, respectively); however, group II (0.5 mg/day E2 + 100 mg/day progesterone) showed a statistically significant difference (p 0.032) in relation to non-users/placebo[31].

d.17-beta-estradiol (E2) + norethisterone acetate (NETA)

Yüksel *et al.,* when comparing users of 17-beta-estradiol (E2) at 2 mg/day + norethisterone acetate (NETA) at 1 mg/day (n = 22) with non-users (n = 21) for six months, noticed weight gain in both groups, albeit with no significant difference between them (HT =+0.68 kg, and control = +0.77 kg)[22].

e.Estradiol valerate + drospirenone or 17-beta-estradiol (E2) + norethisterone acetate (NETA)

Paoletti et al. followed up, for a 12-month period: 1. HT users receiving the combination 1 mg/day estradiol valerate + 3 mg/day drospirenone (n = 36); 2. users of 1 mg/day estradiol (E) + 0.5 mg norethisterone acetate (NETA) (n = 36); 3. patients being given placebo (n = 16). The results showed a weight loss of -1.0 kg in group 1, -0.2 kg in group 2, whereas, in the placebo, there was found a weight increase of +0.2 kg. The results for groups 1 and 2 showed significant differences (p = 0.04 and p = 0.001, respectively) when compared to non-users[29].

In other words, estrogen therapy in the transition and after menopause did not contribute to a statistically significant change in body weight, as seen in most studies. The only combinations that did lead to a change in weight were:

- 0.5 mg/day 17-beta-estradiol (E2) + 100 mg/day progesterone, with a weight increase of 0.7 kg (p 0.032)
- 1 mg/day estradiol valerate + 3 mg/day drospirenone with a weight decrease of -1.0 kg (p = 0.04)
- 1 mg/day estradiol (E) + 0.5 mg norethisterone acetate (NETA), with a weight decrease of -0.2 kg (p = 0.001).

Hormone therapy with tibolone

Ziaei *et al*. evaluated three groups for nine months: I. users of 2.5 mg/day tibolone + 500 mg/day calcium + 200 IU/day vitamin D (n = 46); II. 0.625 mg/day CEE + 2.5 mg/day MPA + 500 mg/day calcium + 200 IU/day vitamin D (n = 6); III. non-HT users: 500 mg/day calcium + 200 IU/day vitamin D (n = 49). group I, after tibolone, showed a weight gain of +0.80 kg (SD ± 1.96); group II showed a weight gain of +0.67 kg (SD ± 2.41); and the control group showed a weight increase of +0.44 kg (SD ± 1.33); however, no group showed significant weight changes (p > 0.05)[28].

Odabasi et al. observed a weight gain (+0.74 kg, SD ± 0.6) in patients using 2.5 mg/day tibolone (n = 19), when compared to individuals in the control group (n = 21), who also showed weight gain (+0.77 kg, SD ± 0.43), but with no significant differences (p = 0.652)[21].

Therefore, tibolone therapy was not associated with weight changes either.

Meta-analysis

For the meta-analysis, we grouped studies with similar methodologies, formulations, and dosages. HT users were divided into two groups and then compared to controls: I. 0.625 mg/day CEE + 2.5 mg/day MPA (Table 3); II. 2.5 mg/day tibolone (Table 4).

Group I did show weight gain (+0.279 kg, CI -1.71 to 2.27), but with no significance when compared to the control group[18, 25, 27].

Group II also showed weight gain (+0.670 kg, CI -1.14 to 2.48) with no significance when compared to the group of non-users[21,23].

The other articles were included as statistical data, given that it was not possible to group them due to the different formulations, dosages, and administration routes of HT.

(See table in next page)

DISCUSSION

The belief that HT can cause weight gain is still widespread among women and physicians, which makes it difficult to prescribe in those very cases involving a required clinical prescription therefor.

The latest systematic review published in 2005 had already contributed significantly to clarifying this issue[12] by demonstrating that, in most RCTs, no significant weight gain had been observed either in patients using estrogen (E) alone in different regimens, dosages, and routes of administration, or in those receiving a combined E + P therapy, when compared to non-users[32].

The present review added another 10 published RCTs. In the articles reporting no differences between non-users and users of HT, the formulations were[18,19,22,25,28,30,31]: estrogens alone (0.625 mg/day conjugated equine estrogen); 2 mg/day 17-beta-estradiol (E2) + 1 mg/day norethindrone acetate (NETA); 1 mg/day E2 + 100 mg/day progesterone; 0.5 mg/day E2 + 50 mg/day progesterone; 0.25 mg/day E2 + 50 mg/day progesterone; 0.625 mg/day CEE + 2.5 mg/day medroxyprogesterone acetate (MPA); 0.45 mg/day CEE + 2.5 mg/day MPA; 0.45 mg/day CEE + 1.5 mg/day MPA; 0.3 mg/day CEE + 1.5 mg/day MPA; 0.625 mg/day EEC + 10 mg/day dydrogesterone; 0.625 mg/day CEE+ 100 mg/day micronized progesterone; 0.3 mg/day CEE + 100 mg/day micronized progesterone; 0.625 mg/day EEC + 500 mg/day calcium + 200 IU/day vitamin D; 2.5 mg/day tibolone + 500 mg/day calcium + 200 IU/day vitamin D.

From the evaluated articles, in general, HT does not appear to cause weight changes in postmenopausal women. However, due to the different HT formulations used across the selected articles, we performed two independent meta-analyses. In the first meta-analysis, articles involving HT users (0.625 mg/day CEE + 2.5 mg/day MPA) and non-users were analyzed and compared; the results showed weight gain in HT users and non-users, but no statistical significance[18,19, 25]. In the second meta-analysis, articles involving users of 2.5 mg/day tibolone were analyzed and compared; the results indicated weight gain, but without significance when compared to those results obtained from non-users[21,23,27].

Limitations

Limitations must be considered, such as the scarcity of studies, the need to disregard 5 of the 15 articles previously selected for their lack in quality and use of different formulations, with different control groups, and different steroid dosages, which precluded us

Table 1: Authors, year of publication, follow-up time (months), intervention (HT), intervention (n) and control groups (n), weight change in the intervention and control groups (Initial weight / Final weight) (Mean±standard deviation).

			INTERVENTION GROUP					CONTROL GROUP				
Authors	**Year**	**T (Months)**	**Intervention (HT)**	**N**	**Initial W (kg) ± SD**	**Final W (kg) ± SD**	**D ± SD**	**Control group**	**N**	**Initial W (kg) ± SD**	**Final W (kg) ± SD**	**D ± SD**
Yasui et al.[17]	2004	12	CEE at 0.625 mg/day + MPA at 2.5 mg/day	74				CEE at 0.625 mg/day + MPA at 2.5 mg/day	63			
Chen et al.[18]	2005	36	CEE at 0.625 mg/day + MPA at 2.5 mg/day	432	73.78 ± 15.01	74.37	0.59	Placebo	390	74.98 ± 16.55	75.08	0.1
Sites et al.[19]	2005	24	CEE at 0.625 mg/day + MPA at 2.5 mg/day	26	64.6 ± 9.1	64.9 ± 8.9	0.3	Placebo	25	66.9 ± 8.8	67.4 ± 9.5	0.5 ± 0.7
Tugrul et al.[20]	2006	12	CEE at 0.625 mg/day + MPA at 2.5 mg/day	139	69.9 ± 11.8	69.8 ± 11.7		E2 at 1 mg/day + NETA at 0.5 mg/day	107	67.6 ± 11.1	67.3 ± 10.9	
Odabasi et al.[21]	2006	6	Tibolone at 2.5 mg/day	19	69.2 ± 2.8		0.74 ± 0.6	Placebo	21	69.5 ± 2.6		0.77 ± 0.43
Yüksel et al.[22]	2006	6	E2 at 2 mg/day + NETA at 1 mg/day	22	72.6 ± 2.1		0.68	Placebo	21	69.5 ± 2.6		0.77
Tommaselli et al.[23]	2006	12	Tibolone at 2.5 mg/day	23	65.4 ± 12.5	65.2 ± 10.4		Women Undergoing No Treatment	21	65.8 ± 10.4	65.9 ± 11.3	
Zang et al.[24]	2006	3	Testosterone undecanoate at 40 mg Estradiol valerate at 2 mg/day	21 22	65.9 ± 8.4 65.5 ± 7.5	66.8 ± 9.2 66.3 ± 7.3		Testosterone undecanoate at 40 mg + Estradiol valerate 2 mg/day	20	66.6 ± 9.4	67.6 ± 9.5	

Continuation - Table 1: Authors, year of publication, follow-up time (months), intervention (HT), intervention (n) and control groups (n), weight change in the intervention and control groups (Initial weight / Final weight) (Mean±standard deviation).

			INTERVENTION GROUP					CONTROL GROUP				
Authors	**Year**	**T (Months)**	**Intervention (HT)**	**N**	**Initial W (kg) ± SD**	**Final W (kg) ± SD**	**D ± SD**	**Control group**	**N**	**Initial W (kg) ± SD**	**Final W (kg) ± SD**	**D ± SD**
Thomeycroft et al.[25]	2006	24	CEE at 0.625 mg/day CEE at 0.625 mg/day + MPA at 2.5 mg/day CEE at 0.45 mg/day CEE at 0.45 mg/day + MPA at 2.5 mg/day CEE at 0.45 mg/day + MPA at 1.5 mg/day CEE at 0.3 mg/day CEE at 0.3 mg/day + MPA at 1.5 mg/day	97 86 95 96 94 89 98	67.1 ± 8.9 65.7 ± 8.9 65.7 ± 8.5 65.4 ± 8.9 67.7 ± 9.4 64.7 ± 8.0 65.3 ± 8.5		1.88 ± 0.92 1.14 ± 0.66 0.32 ± 0.57 1.82 ± 0.5 1.42 ± 0.41 0.23 ± 0.40 1.29 ± 0.47	Placebo	94	64.9 ± 8.9		2.63 ± 0.58
Yüksel et al.[26]	2007	6	Transdermal E2 at 50 µg/day + NETA 0.25 µg/day Transdermal E2 at 50 µg/day + MPA 5 mg/day	19 19	70.9 ± 10.8 69.1 ± 8.7			Transdermal E2 at 1 mg/day + NETA 0.5 mg/day	21	70.6 ± 9.9		
Dedeoglu et al.[27]	2007	6	E2 at 0.625 mg/day + MPA at 2.5 mg/day Tibolone at 2.5 mg/day	31 32	67.5 65.1	68.2 66.3		Control group (did not receive placebo)	34	65.8	68.4	

Continuation - Table 1: Authors, year of publication, follow-up time (months), intervention (HT), intervention (n) and control groups (n), weight change in the intervention and control groups (Initial weight / Final weight) (Mean±standard deviation).

			INTERVENTION GROUP					CONTROL GROUP				
Authors	**Year**	**T (Months)**	**Intervention (HT)**	**N**	**Initial W (kg) ± SD**	**Final W (kg) ± SD**	**D ± SD**	**Control group**	**N**	**Initial W (kg) ± SD**	**Final W (kg) ± SD**	**D ± SD**
Ziaei et al.[28]	2010	9	Tibolone at 2.5 mg/day + Calcium at 500 mg/day + Vit. D at 200 IU/ day CEE at 0.625 mg/day + MPA at 2.5 mg/day + Ca at 500 mg/day + Vit D at 200 IU/day	46 46	66.78 ± 7.63 70.82 ± 8.55		0.8 ± 1.96 0.67 ± 2.41	Calcium at 500 mg/day + Vit D at 200 IU/day	49	69.86 ± 9.12		0.44 ± 1.33
Paoletti et al.[29]	2015	12	Estradiol valerate at 1 mg/day + Drospirenone at 3 mg/day Estradiol at 1 mg/day + NETA at 0.5 mg/day	36 36	59.6 ± 8.1 60 ± 8.3		-1.0 -0.2	Placebo	16	60.9 ± 7.8		0.2
Deng et al.[30]	2018	12	CEE at 0.625 mg/day + Micronized progesterone at 100 mg/day CEE 0.3 mg/day + Micronized progesterone at 100 mg/day	32 36	58.9 ± 9.7 60.9 ± 7.2		-0.1 ± 3 0.1 ± 2	CEE at 0.625 mg/day + Dydrogesterone at 10 mg/day	34	61.1 ± 7.2		-0.6 ± 2.6

Continuation - Table 1: Authors, year of publication, follow-up time (months), intervention (HT), intervention (n) and control groups (n), weight change in the intervention and control groups (Initial weight / Final weight) (Mean±standard deviation).

			INTERVENTION GROUP					CONTROL GROUP				
Authors	**Year**	**T (Months)**	**Intervention (HT)**	**N**	**Initial W (kg) ± SD**	**Final W (kg) ± SD**	**D ± SD**	**Control group**	**N**	**Initial W (kg) ± SD**	**Final W (kg) ± SD**	**D ± SD**
Black et al.[31]	2020	12	E2 at 1 mg/day + Progesterone at 100 mg/day E2 at 0.5 mg/day + Progesterone at 100 mg/day E2 at 0.5 mg/day + Progesterone at 50 mg/day E2 at 0.25 mg/day + Progesterone at 50 mg/day	282 305 312 280	72.1 ± 12.3 71.7 ± 13.1 72.2 ± 11.8 72.1 ± 11.9		0.3 ± 4.4 0.7 ± 4.4 0.5 ± 4.3 0.3 ± 4.2	Placebo	93	71.4 ± 11.5		-0.3 ± 4.3

HT: Hormone Therapy; CEE: Conjugated Equine Estrogen; MPA: Medroxyprogesterone Acetate; E2: 17-beta estradiol; NETA: Norethisterone Acetate; NOMAC: Nomegestrol Acetate; SERM: selective estrogen modulators; W: Weight; kg: Kilogram; SD: Standard deviation.

Table 3. Statistical Analysis – Conjugated Equine Estrogen (CEE) at 0.625 mg/day + Medroxyprogesterone acetate (MPA) 2.5 mg/day compared to Placebo.

					Intervention		Placebo								
Studies	**Year**	**N Intervention**	**N Placebo**	**N Total**	**Gain**	**SD**	**Gain**	**SD**	**MD**	**SE**	**Si**	**Wi**	**MD*Wi**	**SUM MD*Wi**	**Overall**
Chen et al. [18]	2005	432	390	822	0.59	15.01	0.10	16.55	-0.49	1.106	15.759	0.82	-0.400	0.419	0.279
Sites et al.[19]	2005	26	25	51	0.30	9.00	0.50	9.15	0.20	2.542	9.074	0.15	0.031		
Thomeycroft et al.[25]	2006	86	94	180	1.14	9.23	2.63	9.19	1.49	1.374	9.209	0.53	0.789	SUM Wi	SE
														1.501	1.01

Table 4: Statistical Analysis – Tibolone.

Studies	Year	N Pre	N Post	N Total	Before using HT m1	Before using HT SD	After HT m2	After HT SD	MD	SE	Si	Wi	MD*Wi	SUM MD*Wi	Overall
Odabasi et al.[21]	2006	21	21	42	69.20	2.80	69.94	3.40	0.74	0.961	3.114	1.08	0.801	0.784	0.670
Tommaselli et al.[23]	2006	23	23	46	65.40	12.50	65.20	10.40	-0.20	3.391	11.498	0.09	-0.017		
												SUM Wi		1.169	SE
															0.92

from drawing comparisons that would be more accurate. In addition, there was only one article that evaluated estrogen therapy alone, a modality widely used in practice in hysterectomized women.

Ultimately, in any systematic review there is a risk of excluding relevant articles, whether at the time the search strategy is being designed or the articles are being selected.

CONCLUSION

Although it is clear that HT cannot justify weight gain in transition and after menopause, specific studies with estrogen therapy alone are rare. Thus, future research involving estrogen alone should be encouraged, due to its sheer relevance.

The present review, which is an update to the review published by Kongnyuy *et al*.,[12], confirms that, for clinical practice purposes, most HT formulations do not promote weight gain. Nonetheless, there are regimens we included in this study that do show significant changes in the weight of HT users: weight gain with 0.5 mg/day 17-beta-estradiol (E2) + 100 mg/day progesterone versus weight reduction with 1 mg/ day estradiol valerate+ 3 mg/day drospirenone and 1 mg/day estradiol (E) + norethisterone acetate

It is essential that the medical community becomes aware of this so that physicians can prescribe HT based on evidence published in the literature.

Author Contributions

All authors contributed to the manuscript.

Isabela Godoy Murbach: Participated in data collection, data analysis, statistical analysis and writing of the text. Vitória F. de Meo Martins: Participated in data collection, data analysis, statistical analysis and writing of the text. Milena Martello Cristófalo: Participated in the study design, statistical analysis, discussion of results and final version of the text. Érika T. Fukunaga: Participated in the statistical analysis. José Mendes Aldrighi: Participated in the general orientation of the research, definition of the study design, statistical analysis, discussion of results and final version of the text.

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Conflicts of Interest

The authors report no conflict of interest.

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Resumo

Objetivo: realizar uma revisão sistemática e meta-análise para avaliar se a terapia hormonal (TH) aumenta o peso em mulheres na transição menopausal e após a menopausa.

Métodos: este artigo propõe uma atualização da revisão sistemática publicada em 2005 pela Cochrane Library (Kongnyuy EJ *et al.,* 2005) com referência a estudos avaliando mudanças de peso em mulheres recebendo TH de 1986 a 2005. Seguindo as recomendações do PRISMA, incluímos ensaios clínicos randomizados (RCTs) de maio de 2005 em diante do Medline, Embase e dos bancos de dados Cochrane CENTRAL. Diferenças médias padronizadas (SMD) e intervalos de confiança de 95% (IC) foram calculados. Dois autores avaliaram independentemente o risco de vieses nos estudos selecionados.

Resultados: foram incluídos dez ECRs, totalizando 2.588 usuários de HT e 764 não usuários. Diferentes esquemas, dosagens e vias de administração em usuários de HT foram analisados e comparados a não usuários. Os resultados não mostraram diferenças estatisticamente significativas para a maioria dos esquemas de TH avaliados. Houve ganho de peso significativo apenas nos pacientes que usaram apenas EEC nas doses de 0,45 mg/dia e 0,3 mg/dia quando comparados ao placebo (p 0,01); assim como em pacientes recebendo combinações estoprogestativas de 0,5 mg/dia de 17-beta-estradiol (E2) + 100 mg/dia de progesterona, com aumento de peso de 0,7 kg (p 0,032). Por outro lado, as combinações de 1 mg/dia de valerato de estradiol + 3 mg/dia de drospirenona apresentaram redução de -1,0 kg (p = 0,04), enquanto foi identificada redução de -0,2 kg (p = 0,001) nas pacientes que usaram 1 mg /dia estradiol (E) + 0,5 mg de acetato de noretisterona (NETA). A terapia com tibolona não mostrou alterações estatisticamente significativas no peso. Após realizar uma meta-análise, os resultados comparativos entre usuárias e não usuárias mostraram que houve um leve aumento de peso (+0,279 kg ; IC -1,71 a 2,27) em pacientes em uso de 0,625 mg/dia de estrogênio equino conjugado (CEE) + 2,5 mg/dia de acetato de medroxiprogesterona (MPA). Quanto aos pacientes que receberam Tibolona 2,5 mg/dia, também foi observado ganho de peso (+0,670 kg; IC de -1,14 a 2,48). No entanto, esses aumentos não foram significativos quando comparados aos não usuários de HT.

Conclusões: a maioria dos esquemas estudados mostrou que as pacientes em uso de TH na transição menopausal e após a menopausa não apresentaram ganho de peso significativo. A única combinação que apresentou ganho de peso foi 0,5 mg/dia de 17-beta-estradiol (E2) + 100 mg/dia de progesterona, enquanto houve redução de peso nas pacientes que usaram 1 mg/dia de valerato de estradiol + 3 mg/dia de drospirenona e 1 mg/dia estradiol (E) + acetato de noretisterona.

Palavras-chave: pós-menopausa; menopausa, climatério, terapia de reposição hormonal, índice de massa corporal, peso corporal