Climacteric

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: https://www.tandfonline.com/loi/icmt20

Impact of micronized progesterone on body weight, body mass index, and glucose metabolism: a systematic review

A. Coquoz, C. Gruetter & P. Stute

To cite this article: A. Coquoz, C. Gruetter & P. Stute (2019) Impact of micronized progesterone on body weight, body mass index, and glucose metabolism: a systematic review, Climacteric, 22:2, 148-161, DOI: 10.1080/13697137.2018.1514003

To link to this article: https://doi.org/10.1080/13697137.2018.1514003

Published online: 27 Nov 2018.

CLIMACTERIC
2019, VOL. 22, NO. 2, 148–161
https://doi.org/10.1080/13697137.2018.1514003

Taylor & Francis
Taylor & Francis Group

REVIEW

Impact of micronized progesterone on body weight, body mass index, and glucose metabolism: a systematic review

A. Coquoz[a], C. Gruetter[b] and P. Stute[a]

[a]Department of Obstetrics and Gynecology, University of Bern, Bern, Switzerland; [b]Department of Internal Medicine, Bürgerspital Solothurn, Solothurn, Switzerland

ABSTRACT

In women, body weight increases with age. Often menopausal hormone therapy (MHT) is blamed for enhancing this effect. In recent years, the debate on bioidentical MHT including micronized progesterone (MP) has increased. Among others, the question has been raised of whether MHT containing MP has an impact on body weight and glucose metabolism. Based on a systematic literature review on the impact of MHT containing MP on body weight, body mass index (BMI), and glucose metabolism, the following conclusions can be drawn: estrogens combined with MP (1) either do not change or reduce body weight in normal weight postmenopausal women, (2) do not change BMI in normal and overweight postmenopausal women, (3) do not change or improve fasting serum glucose levels in (non-)diabetic postmenopausal women, (4) do not change or improve fasting serum insulin levels in (non-)diabetic postmenopausal women, and (5) do not have an impact on serum glycated hemoglobin in postmenopausal diabetic women. This beneficial effect is probably mostly due to the estrogen MHT component.

ARTICLE HISTORY
Received 20 January 2018
Revised 6 August 2018
Accepted 14 August 2018

KEYWORDS
Micronized progesterone; menopause; body weight; body mass index; glucose metabolism; hormone therapy

Introduction

The steroid hormone progesterone plays a key role in female reproduction[1]. For therapeutic reasons, micronized progesterone (MP) can be used, for example, for endometrial protection when estrogens are applied in menopausal women with an intact uterus[2]. Many women gain weight while ageing and during menopause[3]. They are also afraid that menopausal hormone therapy (MHT) may even accelerate this process although the opposite has been found to be true[4]. The aim of this systematic literature review was to assess the impact of estrogens combined with MP on body weight, body mass index (BMI), and glucose metabolism.

Materials and methods

In May 2017, a systematic literature search was performed using the database Medline (PubMed). To be included, the study population had to be exposed to MP. The trials' outcomes had to include body weight, BMI, serum insulin, glucose, glycated hemoglobin (HbA1c), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), or the quantitative insulin sensitivity index (QUICKI). All clinical trials published in English, French, and German were included. We applied a study duration restriction of at least 3 months and a sample size restriction of at least 20 women. All women had to be postmenopausal. In a first step, the database was searched by combining the term 'micronized progesterone' and many keywords and Mesh terms including 'body weight', 'BMI', 'body composition', 'glucose', 'insulin', 'HbA1c', and 'HOMA'. The terms were always combined with the logical connective 'AND'. All titles and abstracts were screened and suitable publications were read in full length. To make sure no relevant studies were left out, related citations and important references to the subject were included if they matched the inclusion criteria. Estrogen dosages were classified as high dose, standard dose, low dose, and ultralow dose according to the definition of the International Menopause Society[5] (Figure 1).

Results

The systematic literature search yielded 612 hits in total. Thereof, 18 studies fulfilled the inclusion criteria and were included in the review[6–23] (Table 1). The five largest studies and their outcomes are presented in Figures 2 and 3, respectively. The sample size ranged from 20 to 875 women being postmenopausal in all studies. Treatment duration ranged from 3 months to 3 years.

The impact of micronized progesterone on body weight

The impact of MP combined with estrogens on body weight was assessed in 10 studies[6–8,10,11,13,14,19,20,23]. Of those, three studies reported a significant impact on body weight[8,10,11] while seven did not[6,7,13,14,19,20,23]. The studies showing an impact on body weight were either prospective cohort studies[8,11] or a randomized placebo-controlled trial (PC-RCT)[10], comprising 26[11] to 847[10] postmenopausal women. Study

CONTACT Petra Stute petra.stute@insel.ch Department of Gynecologic Endocrinology and Reproductive Medicine, University Clinic of Obstetrics and Gynecology, Inselspital Berne, Effingerstrasse 102, 3010 Berne, Switzerland

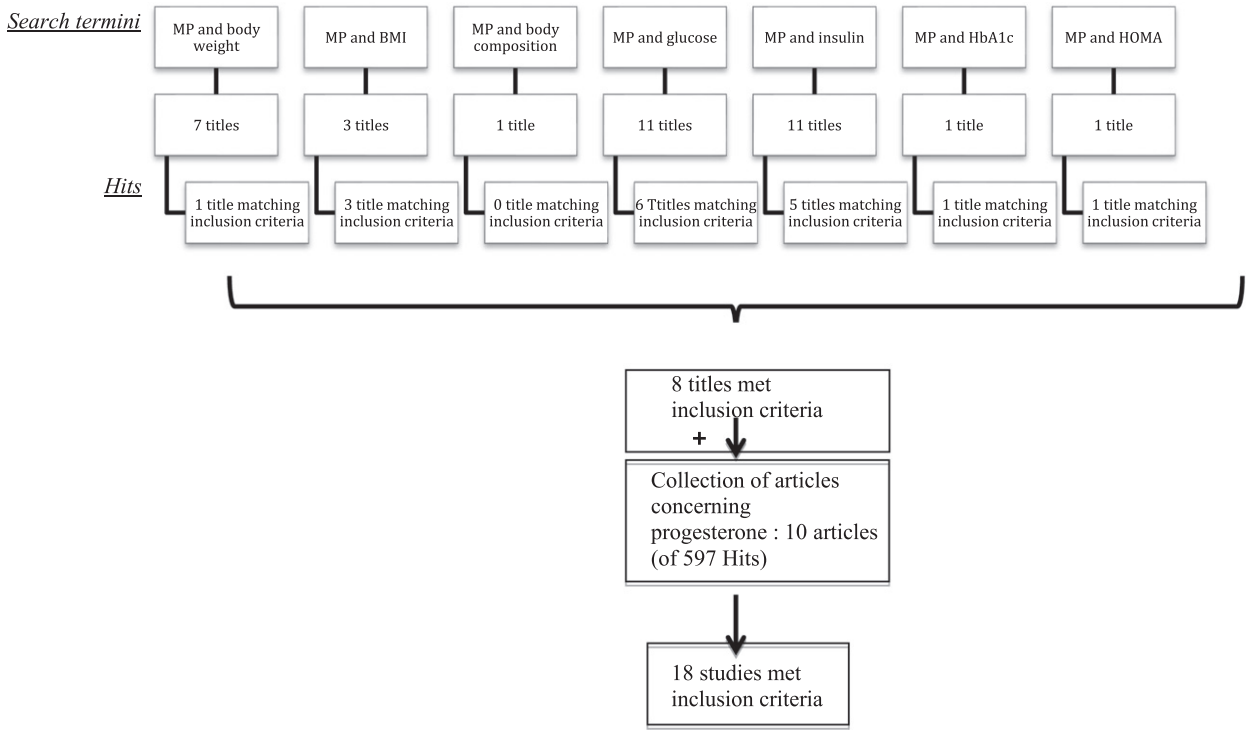

Figure 1. Literature search strategy. BMI, body mass index; HbA1c, glycated hemoglobin; HOMA, Homeostasis Model Assessment; MP, micronized progesterone.

duration ranged from 1 year[11] to 3 years[8,10]. MHT contained either oral[10] or transdermal[8,11] estrogens at standard dose. MP was combined either sequentially[10] or continuously[8,11]. The route of application was either oral at 200 mg/day[10], vaginal at 100 mg/day every other day[8], or 45 mg/day twice a week[11]. One study used oral medroxyprogesterone acetate (MPA) either sequentially or continuously as a comparator to MP[10]. At study baseline, the mean body weight was within the normal range[8,10,11].

In the first study, body weight was significantly decreased after 36 months of treatment (−0.6 kg)[8]. Similarly, in the second study, body weight was significantly decreased after 6 months (−0.7 kg) and slightly decreased further afterward (−0.8 kg after 9 months)[11]. Within the PC-RCT, MP containing combined MHT was compared to MPA containing combined MHT and placebo[10]. Body weight gain in the active treatment arms ranged from 0.7 kg (unopposed estrogen therapy with conjugated equine estrogen (CEE)) to 1.3 kg (CEE combined with either MPA or MP) after 3 years of treatment without displaying a significant intergroup difference. In contrast, women receiving placebo gained more weight during the follow-up, although the effect was small (1 kg across 3 years) ($p = 0.006$ placebo vs. MHT).

The studies showing no impact on body weight were either a prospective observational cohort study[23], randomized head-to-head trials[6,19], or PC-RCTs[7,14,20] including one cross-over randomized trial[13]. Cohort sizes ranged from 25[14] to 875[20] postmenopausal women. Study duration was from 3 months[6] to 3 years[20]. MHT contained either oral[13,19,20,23], intranasal[6,13], or transdermal[6,7,13,14] estrogens at a standard dose[6,14,19,20,23] or high dose[7]. MP was combined sequentially[6,7,13,14,19,20,23]. The route of application was either oral at 100 mg/day[19] or 200 mg/day[7,14,19,20], or vaginal at 200 mg/day[6,13,23]. At study baseline, mean body weight was within the normal range[6,7,13,14,19,20,23]. One study used oral MPA either sequentially or continuously as a comparator to MP[20].

The impact of micronized progesterone on BMI

The impact of MP combined with estrogens on BMI was assessed in seven studies[6,9,12,13,15,21,22]. At study baseline, mean BMI was below 30 kg/m^2 [6,9,12,13,15,21,22]. None of them reported a significant change in BMI.

In detail, studies assessing BMI change were either a prospective observational cohort study[15] or randomized head-to-head trials[6,9,12,13,21,22] including cross-over randomized trials[13,21,22]. Sample sizes ranged from 21[21] to 86[6,13] postmenopausal women. Study duration was from 3 months[6] to 3 years[15]. MHT contained either oral[13,21,22], transdermal[6,9,12,13,15,21], or nasal[6,13,22] estrogens at a standard dose[6,9,12,13,21,22], low dose[13,22], or ultralow dose[15]. MP was combined either sequentially[6,9,12,13,21,22] or continuously[15]. The route of application was either oral at 100 mg/day[9], 200 mg/day[9,12], or 300 mg/day[21], vaginal at 100 mg/day[9] or 200 mg/day[6,9,13,22], or transdermal at 20–60 mg/day[15]. MHT containing MP was compared to other MHT preparations containing progestins such as MPA[12], nomegestrol acetate[12], dydrogesterone[12], or drospirenone (DRSP)[22], respectively. There were no group differences for BMI between combined MHT containing MP or progestins, respectively.

The impact of micronized progesterone on glucose metabolism

The impact of MP combined with estrogens on serum glucose, insulin, HOMA-IR, and HbA1c levels was assessed in 11 studies[6,13–18,20–23]. Blood samples were collected after a

Table 1. Overview of studies included in the review.

Reference	*Study design*	*Sample size*	*Study duration*	*Estrogen*	*Progestogen*	*BMI (kg/m²)*	*Body weight (kg)*	*Serum insulin (μU/ml)*	*Serum glucose (mg/dl)*	*HbA1c (%), HOMA-IR and QUICKI*	*Results*
Casanova and Spritzer[6]	RCT	86 postmenopausal women: Group 1, $n = 40$; Group 2, $n = 46$	3 months	Group 1: intranasal E2 3 mg/day for 2 months	Vaginal MP 200 mg/day (14 days/month)	Baseline: intranasal, 26 ± 3; transdermal, 26 ± 3 After E2: intranasal, 26 ± 3; transdermal: 26 ± 3	Baseline: intranasal, 66 ± 7; transdermal, 64 ± 9	Baseline: intranasal, 7 (4–10); transdermal, 6 (3–9) After E2: intranasal, 6 (2–8); transdermal, 7 (3–9)	Fasting glucose/2-h glucose Baseline: intranasal, 91 ± 11/106 ± 29; transdermal, 92 ± 9/102 ± 23 After E2: intranasal, 91 ± 8/113 ± 38; transdermal, 91 ± 8/103 ± 35		No significant change: BMI ($p = 0.8$), body weight ($p = 0.7$), serum glucose ($p = 0.2$), serum insulin ($p = 0.2$)
				Group 2: transdermal E2 1.5 mg/day for 3 months							
						After E2 + MP: intranasal, 26 ± 3; transdermal, 26 ± 3 ($p = 0.6$)	After E2: intranasal, 66 ± 7; transdermal, 64 ± 9 After E2 + MP: intranasal, 66 ± 7; transdermal, 64 ± 10 ($p = 0.6$)	After E2 + MP: intranasal, 6 (4–9); transdermal, 7 (3–9) ($p = 0.2$)	After E2 + MP: intranasal, 93 ± 11/110 ± 39; transdermal, 91 ± 10/101 ± 31		
Hassager and Christiansen[7]	PC-RCT	45 postmenopausal women: Group 1, $n = 20$; Group 2, $n = 25$	2 years	Group 1: oral E2-valerate 2 mg/day on days 1–11; oral E2-valerate 2 mg/day + oral CPA 1 mg/day on days 12–21; no treatment on days 22–28	Group 3: vaginal MP 200 mg/day on days 13–24 during the 2nd year		Group 1: 0.24 ± 0.39				No significant change in body weight
				Group 2: oral placebo			Group 3: 0.48 ± 0.32				
				Group 3: transdermal E2 (0.6 mg E2/g cream) 5 g/day on days 1–24, no treatment on days 25–28			Groups 2 + 4 (placebo): 0.83 ± 0.18				
				Group 4: placebo cream							
Cicinelli *et al.*[8]	Prospective cohort study	30 postmenopausal women	3 years	Transdermal E2 1.5 mg/day	Oral MP 100 mg every other day		Baseline, 66.7 ± 7.0; Month 36, 66.1 ± 7.3				Significant decrease in body weight at month 36 ($p < 0.5$)

(*continued*)

Table 1. Continued.

Reference	Study design	Sample size	Study duration	Estrogen	Progestogen	BMI (kg/m^2)	Body weight (kg)	Serum insulin (μU/ml)	Serum glucose (mg/dl)	HbA1c (%), HOMA-IR and QUICKI	Results
Di Carlo *et al.*[9]	RCT	80 postmenopausal women	12 cycles (28 days each)	All groups: transdermal E2 50 μg/day	Group A: oral MP 100 mg/day on days 14–25	Group A: baseline, 24.5 ± 2.2; after 12 cycles, 24.6 ± 2.8					No significant change in BMI
					Group B: oral MP 200 mg/day on days 14–25	Group B: baseline, 24.9 ± 2.3; after 12 cycles, 24.9 ± 2.5					
					Group C: vaginal MP 100 mg/day on days 14–25	Group C: baseline, 25.2 ± 2.0; after 12 cycles, 25.7 ± 2.1					
					Group D: vaginal MP 200 mg/day on days 14–25	Group D: baseline, 24.2 ± 2.5; after 12 cycles, 24.1 ± 2.9					
Espeland *et al.*[10]	PC-RCT	847 postmenopausal women: Group 1 = 166, Group 2 = 170, Group 3 = 169, Group 4 = 170, Group 5 = 172	3 years	Group 1: placebo	Groups 1 + 2: placebo		Group 1: 2.1 ± 0.4				No significant difference between the active treatment arms (groups 2–5: $p = 0.74$); women with placebo gained more weight than women with an active therapy ($p = 0.006$)
				Groups 2–5: oral CEE 0.625 mg/day	Group 3: oral MPA 2.5 mg/day		Group 2: 0.7 ± 0.4 Group 3: 1.3 ± 0.4				
					Group 4: oral MPA 10 mg/day on days 1–12		Group 4: 0.9 ± 0.3				

(*continued*)

Table 1. Continued.

Reference	Study design	Sample size	Study duration	Estrogen	Progestogen	BMI (kg/m^2)	Body weight (kg)	Serum insulin (μU/ml)	Serum glucose (mg/dl)	HbA1c (%), HOMA-IR and QUICKI	Results
					Group 5: oral MP 200 mg/day on days 1–12		Group 5: 1.3 ± 0.3				
Cicinelli *et al.*[11]	Prospective cohort study	26 postmenopausal women	1 year	Transdermal E2 50 μg/day	Vaginal MP 45 mg twice weekly		Basal month, 65 ± 7.2; 3 months, 64.7 ± 6.9 ($p < 0.05$); 6 months, 64.3 ± 6.6 ($p < 0.005$); 9 months, 64.2 ± 6.6 ($p < 0.005$); 12 months, 64.5 ± 6.9 ($p < 0.05$)				Significant body weight reduction after 12 months of therapy (decrease during the first 6 months, then stable body weight)
Di Carlo *et al.*[12]	RCT	79 postmenopausal women	12 cycles (28 days each)	All groups: transdermal E2 50 μg/day	Group A: oral MPA 10 mg/day	Group A: baseline, 24.9 ± 2.1; after 12 cycles, 23.6 ± 1.8					No significant change in BMI
					Group B: oral NOMAC 5 mg/day	Group B: baseline, 25.2 ± 2.5; after 12 cycles, 24.8 ± 2.6					
					Group C: oral DYD 10 mg/day	Group C: baseline, 24.1 ± 1.9; after 12 cycles, 25.8 ± 1.3					
					Group D: oral MP 200 mg/day	Group D: baseline, 24.7 ± 2.3; after 12 cycles, 24.0 ± 1.5					
					for all groups on days 14–25						
Casanova *et al.*[13]	Cross-over randomized trial	86 postmenopausal women:	6 months	Group 1, oral E2 1 mg/day; Group 2, transdermal	Group 1: DRSP 2 mg/day	Baseline, 26.2 ± 3; Group 1,	Baseline, 65.4 ± 8.2; Group 1, 65.5 ± 8.2;	Baseline, 6.9 (3.9–9.8); Group 1, 7.2 (4.2–10.2);	Fasting glucose (mg/dl): baseline, 91.9 ± 10; Group 1,		No significant change in BMI, body weight, fasting serum

(*continued*)

Table 1. Continued.

Reference	Study design	Sample size	Study duration	Estrogen	Progestogen	BMI (kg/m^2)	Body weight (kg)	Serum insulin (μU/ml)	Serum glucose (mg/dl)	HbA1c (%), HOMA-IR and QUICKI	Results
		Group 1, $n = 44$; Group 2, $n = 42$		E2 gel 1.5 mg/day or an equivalent dose for nasal route		26.1 ± 3.1; Group 2, 26.2 ± 3 ($p = 0.5$)	Group 2, 65.4 ± 8.2 ($p = 0.3$)	Group 2, 7 (3.8–9.1) ($p = 0.1$)	93 ± 11; Group 2, 92.5 ± 11.3 ($p = 0.3$)		glucose, or insulin concentrations
				After 3 months participants were switched to the other group without washout phase	Group 2: vaginal MP 200 mg/day on 14 days/month						
Mosnier-Pudar *et al.*[14]	PC-RCT	25 postmenopausal, women with non-insulin-dependent diabetes mellitus: Group 1, $n = 14$; Group 2, $n = 11$	6 months	Group 1: transdermal E2 gel 1.5 mg/day for 21 days (followed by 7 days without medication)	Group 1: oral MP 200 mg/day on days 8–21		Group 1: baseline, 76.3 ± 3.9; Month 1, 77.4 ± 4.4; Month 3, 77.7 ± 4.5; Month 6, 76.6 ± 4.9			HbA1c (%) – Group 1: baseline, 7.1 ± 0.3; Month 3, 6.8 ± 0.2; Month 6, 7.1 ± 0.3	No significant intergroup and intragroup difference in body weight and serum HbA1c levels
				Group 2: no treatment	Group 2: no treatment		Group 2: baseline, 73.4 ± 3.9; Month 1, 74 ± 4; Month 3, 73.8 ± 3.5; Month 6, 72.7 ± 4			Group 2: baseline, 7.8 ± 0.2; Month 3, 8.2 ± 0.2; Month 6, 7.6 ± 0.3	
Stephenson *et al.*[15]	Prospective cohort study	58 postmenopausal women	3 years	Transdermal Bi-Est 0.25–0.5 mg/day for 8 weeks (dosage chosen based on serum hormone levels), then dosage adjustments made; after 8 weeks, some women also received transdermal DHEA 1–2 mg/day and/or transdermal testosterone 0.2–0.5 mg/day	Transdermal MP 20–60 mg/day for 8 weeks (dosage was chosen based on serum hormone levels), then dosage adjustments were made	Baseline, 26.66 ± 4.1; follow-up, 26.49 ± 4.65 ($p = 0.84$)			Fasting glucose (mg/dl): baseline, 107.2 ± 24.8; follow-up, 89.96 ± 16.8 ($p < 0.001$)	HOMA-IR: baseline, 1.97 ± 2.45; follow-up, 1.43 ± 1.18 ($p = 0.16$)	No significant change in BMI and serum HOMA-IR level. Significant decrease in serum fasting glucose level

(*continued*)

Table 1. Continued.

Reference	Study design	Sample size	Study duration	Estrogen	Progestogen	BMI (kg/m^2)	Body weight (kg)	Serum insulin (μU/ml)	Serum glucose (mg/dl)	HbA1c (%), HOMA-IR and QUICKI	Results
Espeland *et al.*[16]	PC-RCT	788 postmenopausal women	3 years	Group 1, Placebo; Groups 2–5, oral CEE 0.625 mg/day	Group 3, oral MPA 2.5 mg/day; Group 4, oral MPA 10 mg/day on days 1–12; Group 5, oral MP 200 mg on days 1–12			Serum insulin (%): mean changes from baseline, after a 75 g OGTT: 12 months/36 months – Group 1 (placebo): Fasting, 7.5 ± 8.2 / 15.3 ± 9.0; 1 h, −2.3 ± 5.2/ −9.4 ± 6.2; 2 h, 0.8 ± 5.8/−9.3 ± 6.2 Group 2 (CEE only): fasting, −6.3 ± 7.9/ −5.6 ± 8.6; 1 h, 0.6 ± 6.0/ −19.5 ± 5.7; 2 h, 4.1 ± 6.8/−1.2 ± 7.4 Group 3 (CEE + continuous MPA): fasting, −18.0 ± 6.3/ −9.3 ± 6.2; 1 h, 1.8 ± 4.8/ −15.1 ± 4.3; 2 h, 10.0 ± 6.6 / −4.6 ± 5.7	Serum glucose (mmol/l): mean changes from baseline, after a 75 g OGTT: 12 months / 37 months – Group 1 (placebo): Fasting, −0.012 ± 0.037/ −0.061 ± 0.048; 1 h, −0.346 ± 0.147/ −0.342 ± 0.175; 2 h, 0.176 ± 0.147 / 0.097 ± 0.0156 Group 2 (CEE only): fasting, −0.155 ± 0.033/ −0.189 ± 0.058; 1 h, 0.080 ± 0.164/ 0.150 ± 0.189; 2 h, 0.106 ± 0.142/ 0.359 ± 0.188 Group 3 (CEE + continuous MPA): fasting, 0.094 ± 0.029/ −0.186 ± 0.031; 1 h, 0.061 ± 0.145/ 0.167 ± 0.144; 2 h, 0.294 ± 0.122/ 0.538 ± 0.123		Groups 1–5, decrease in serum insulin levels at 36 months; Groups 2–5, reduction of fasting insulin (16.1%), fasting glucose (0.122 mmol/l), and increase in 2-h glucose (0.355 mmol/l) compared with placebo. No significant differences between estrogen alone versus opposed estrogen. No significant differences between MPA versus MP ($p = 0.48$). No significant differences between sequential versus continuous MPA ($p = 0.18$) Significant differences between placebo and active therapy ($p < 0.0001$)
								Group 4 (CEE + sequential MPA): fasting, 0.5 ± 7.8/10.7 ± 8.3; 1 h, −7.5 ± 4.5/ −19.1 ± 5.7; 2 h, 11.9 ± 6.3/ −2.0 ± 6.2 Group 5 (CEE + sequential MP): fasting, −14.8 ± 6.4/ −8.5 ± 5.8; 1 h, −7.8 ± 3.7/ −19.6 ± 4.0; 2 h, −1.4 ± 5.5/ −13.9 ± 5.3	Group 4 (CEE + sequential MPA): fasting, −0.108 ± 0.037/ −0.237 ± 0.039; 1 h, −0.093 ± 0.159/ 0.001 ± 0.182; 2 h, 0.356 ± 0.117/ 0.568 ± 0.144 Group 5 (CEE + sequential MP): fasting, −0.105 ± 0.033/ −0.163 ± 0.045; 1 h, −0.132 ± 0.153/		The impact of MHT was most beneficial among women with elevated baseline levels of 1-h glucose ($p = 0.006$) and fasting insulin ($p = 0.01$) but did not vary by baseline serum levels of 1-h insulin, 2-h insulin, fasting glucose or 2-h glucose.

(*continued*)

Table 1. Continued.

Reference	Study design	Sample size	Study duration	Estrogen	Progestogen	BMI (kg/m^2)	Body weight (kg)	Serum insulin (μU/ml)	Serum glucose (mg/dl)	HbA1c (%), HOMA-IR and QUICKI	Results
									−0.229 ± 0.184; 2 h, 0.146 ± 0.112/ 0.269 ± 0.147		
Bolaji *et al.*[17]	Prospective cohort study	32 postmenopausal women	1 year	Oral CEE 0.625 mg/day	Oral MP 100 mg/day on days 1–23/month				Fasting serum glucose (mmol/l): baseline, 4.8 ± 1.24; 6 months, 4.7 ± 0.74; 9 months, 4.4 ± 0.8; 12 months, 5.0 ± 1.07		No significant change in serum glucose levels
Spritzer *et al.*[18]	Prospective cohort study	20 postmenopausal women with treated hypertension	1 year	Transdermal E2 gel 1.5 mg/ day on 21 days/month	Vaginal MP 100 mg/day on 21 days/month				Fasting glucose (mg/dl): before antihypertensive medication, 91 ± 2; before MHT, 93 ± 2; 3 months of MHT, 96 ± 3; 6 months of MHT, 94 ± 2; 12 months of MHT, 97 ± 3; 3 months after MHT, 95 ± 3 ($p = 0.82$)		No significant change in fasting serum glucose level
Darj *et al.*[19]	RCT	30 postmenopausal women	4 months	Oral E2 2 mg/ day on 25 days/month	Group 1, oral MP 50 mg/ day; Group 2, oral MP 100 mg/day; Group 3, oral MP 200 mg/day, each on 25 days/month		Baseline, 65.7; after 4 months, 64.7				No significant change in body weight
The Writing Group for the PEPI Trial[20]	PC-RCT	875 postmenopausal women	3 years	Group 1, placebo; Group 2–5, oral CEE, 0.625 mg/day	Group 3, oral MPA 10 mg/ day on 12 days/month; Group 4, oral MPA 2.5 mg/ day; Group 5, oral MP 200 mg/day on 12 days/month		Baseline / mean change: Group 1, 70.2 ± 3.4/1.3; Group 2, 70.1 ± 1.0/0.4; Group 3, 69.0 ± 1.0/0.8; Group 4, 69.5 ± 0.9/0.6; Group 5, 68.8 ± 1.0/0.6 ($p = 0.79/0.03$)	Fasting Insulin (pmol/l): baseline / mean change – Group 1, 36.6 ± 2.1/3.8; Group 2, 34.0 ± 2.1/−1.7; Group 3, 34.5 ± 2.1/1.3; Group 4, 36.6 ± 2.1/−3.8; Group 5, 34.8 ± 2.1/−3.5 ($p = 0.85$ / 0.07); 2-h insulin (pmol/L): baseline / mean	Fasting glucose (mmol/l): baseline / mean change – Group 1, 5.38 ± 0.04/−0.02; Group 2, 5.41 ± 0.04/−0.16; Group 3, 5.34 ± 0.03/−0.15; Group 4, 5.42 ± 0.04/−0.11; Group 5, 5.40 ± 0.40/−0.14 ($p = 0.68/0.03$); 2-h glucose (mmol/l): baseline / mean		Mean changes in 2-h insulin did not differ significantly between the five groups. Significant increase in 2-h glucose in women with an active treatment compared with placebo ($p = 0.1$): only statistically significant ($p < 0.05$) in women with

(*continued*)

Table 1. Continued.

Reference	Study design	Sample size	Study duration	Estrogen	Progestogen	BMI (kg/m^2)	Body weight (kg)	Serum insulin (μU/ml)	Serum glucose (mg/dl)	HbA1c (%), HOMA-IR and QUICKI	Results
								change – Group 1, 331.8 ± 20.4/−13.7; Group 2, 303.8 ± 19.1/−8.0; Group 3, 313.8 ± 19.1/13.4; Group 4, 301.9 ± 17.4/1.2; Group 5, 312.6 ± 18.7/−25.1 ($p = 0.82/0.29$)	change – Group 1, 6.27 ± 0.14/−0.00; Group 2, 6.52 ± 0.17/0.11; Group 3, 6.08 ± 0.13/0.42; Group 4, 6.46 ± 0.18/0.39; Group 5, 6.27 ± 0.15/0.17 ($p = 0.29/0.01$)		CEE + MPA (sequential or continuous). Women with CEE + MPA (sequential or continuous) had the biggest increase. No significant change in fasting insulin. Significant decrease in fasting glucose in all active treatment arms ($p = 0.03$). The difference between unopposed CEE and placebo was also significant ($p < 0.04$). Significant change in weight only between placebo and unopposed CEE ($p = 0.3$)
Araujo *et al.*[21]	Prospective randomized crossed-over study	21 postmenopausal women with type 2 diabetes mellitus	15 months	Group 1 ($n = 10$), transdermal E2 50 μg/day for 6 months; Group 2 ($n = 11$), oral CEE 0.625 mg/day for 6 months before crossover washout period of 12 weeks	Groups 1 + 2, oral MP 300 mg/day on 12 days/month	Group 1: before treatment, 26.6 ± 2.2; after treatment, 26.8 ± 2.1; Group 2: before, 26.7 ± 2.2; after, 27.0 ± 2.2		Fasting insulin (mU/l) – Group 1: before treatment, 11.5 ± 6.0; after treatment, 12.7 ± 5.6 (p non-significant); Group 2: before treatment, 13.0 ± 7.1; after treatment, 12.9 ± 5.7 (p non-significant)	Fasting glucose (mg/dl) – Group 1: before treatment, 128.7 ± 18.6; after treatment, 128.3 ± 33.4 (p non-significant) Group 2: before treatment, 126.4 ± 17.5; after treatment, 134.5 ± 34.0 (p non-significant)	HOMA-IR – Group 1: before treatment, 3.8 ± 2.0; after treatment, 3.6 ± 1.4 (p non-significant); Group 2: before treatment, 3.5 ± 1.6; after treatment, 4.2 ± 1.9 (p non-significant) HbA1c – Group 1: before	No significant change in BMI. No significant change in fasting serum glucose, insulin, HOMA scores and HbA1c

(*continued*)

Table 1. Continued.

Reference	Study design	Sample size	Study duration	Estrogen	Progestogen	BMI (kg/m^2)	Body weight (kg)	Serum insulin (μU/ml)	Serum glucose (mg/dl)	HbA1c (%), HOMA-IR and QUICKI	Results
										treatment, 6.5 ± 0.7; after treatment, 6.7 ± 1.5 (p non-significant); Group 2: before treatment, 6.6 ± 0.7; after treatment, 6.4 ± 1.5 (p non-significant)	
Casanova *et al.*[22]	Prospective randomized crossed-over study	40 postmenopausal women	4 months	Group 1 ($n = 20$), oral E2 1 mg/day for 2 months; Group 2 ($n = 20$), intranasal E2 3 mg/day for 2 months. Then patients were crossed-over without washout	Group 1, oral DRSP 2 mg/day for 2 months; Group 2, vaginal MP 200 mg/day on 14 days/month. Then patients are crossed-over without washout	Baseline, 26.9 ± 2.6; Group 1, 26.9 ± 2.7; Group 2, 26.9 ± 2.6 ($p = 0.9$)		Baseline, 7.5 (4.7–10.2); Group 1, 6.9 (5.3–11-2); Group 2, 6.4 (5.4–8.9) ($p = 0.3$)	Fasting glucose (mg/dl) – baseline, 91 ± 11; Group 1, 94 ± 13; Group 2, 93 ± 11 ($p = 0.2$)		No significant changes in BMI, serum insulin, and fasting glucose. Non-oral treatment: no changes in serum insulin and glucose levels for estrogen alone versus estrogen + vaginal MP (insulin, $p = 0.1$/glucose, $p = 0.4$)
Bolaji *et al.*[23]	Prospective, cohort study	32 postmenopausal women	1 year	Oral CEE 0.625 mg/day	Oral MP 100 mg/day on 23 days/month						No significant change in weight and serum glucose

Bi-Est, 80% estriol and 20% estradiol; BMI, body mass index; CEE, conjugated equine estrogen; CPA, cyproterone acetate; DHEA, dehydroepiandrosterone; DRSP, drospirenone; DYD, dydrogesterone; E2, estradiol; HbA1c, glycated hemoglobin; HOMA-IR, Homeostasis Model of Insulin Resistance; MHT, menopausal hormone therapy; MP, micronized progesterone; MPA, medroxyprogesterone acetate; NOMAC, nomegestrol acetate; OGTT, oral glucose tolerance test; PC, placebo controlled; QUICKI, quantitative insulin sensitivity index; RCT, randomized controlled trial.

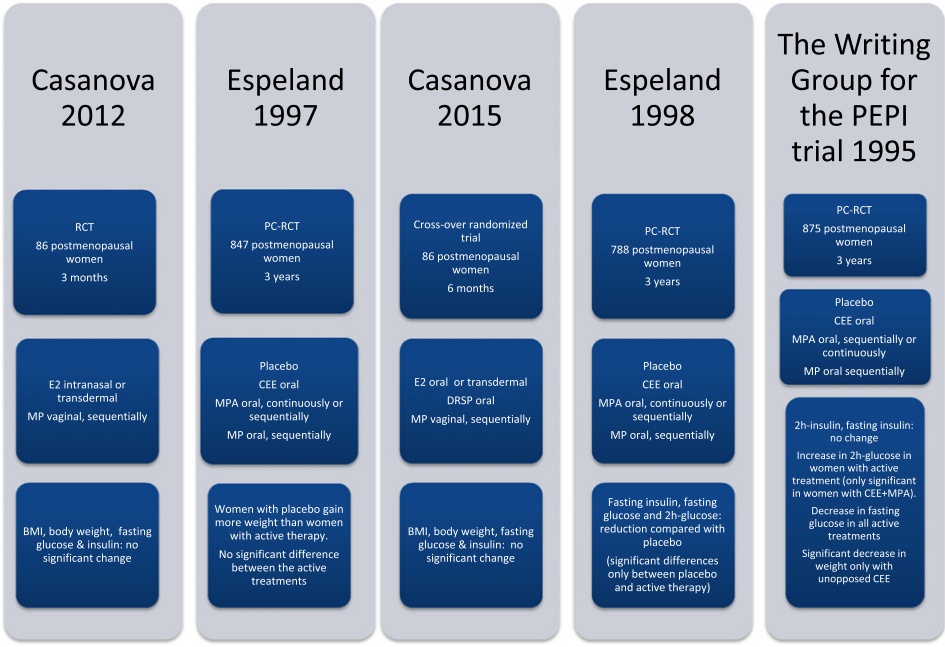

Figure 2. Overview of the study designs of the five largest studies. BMI, body mass index; CEE, conjugated equine estrogen; DRSP, drospirenone; E2, estradiol; MP, micronized progesterone; MPA, medroxyprogesterone acetate; PC-RCT, randomized placebo-controlled trial.

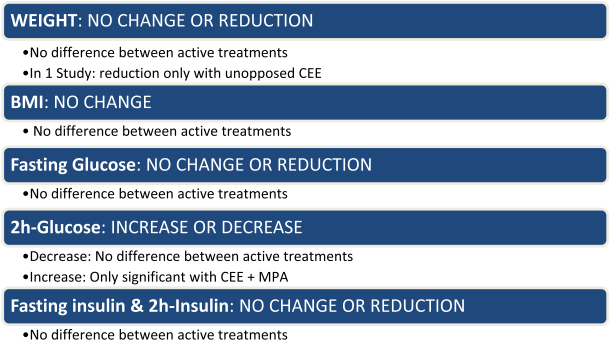

Figure 3. Overview of the outcomes of the five largest studies. BMI, body mass index; CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate.

12-h fast[6,16–18,21] or an overnight fast[13,15,20,22]. The fasting duration was not specified in one study[23]. Serum glucose levels were measured by colorimetric-enzymatic methods[6,13,16,18,20,22] or glucose oxidase method on a Beckman glucose analyzer[21] (not specified in one study[23]). Insulin serum levels were measured by electrochemiluminescence immunoassay[6,13,16,20,22] or radioimmunoassay[21] (not specified in one study[23]). Serum HbA1c levels were determined using ion-exchange liquid chromatography[14,21]. Insulin resistance was assessed by HOMA-IR, using the values of serum fasting insulin and fasting glucose.

The impact of MP combined with estrogens on fasting serum glucose was assessed in 10 studies[6,13,15–18,20–23]. Of those, three studies[15,16,20] reported a significant impact on fasting glucose while seven did not[6,13,17,18,21–23]. The studies showing an impact on fasting glucose were a prospective study[15] or PC-RCTs[16,20], comprising between 58[15] and 875[20] postmenopausal women. Study duration was 3 years[15,16,20]. MHT contained oral estrogens[16,20] at a standard dose or transdermal estrogens[15] at an ultralow dose. MP was either taken orally, sequentially combined at 200 mg/day[16,20], or transdermally, continuously combined at 20–60 mg/day for 8 weeks (then adjustments were made)[15]. Oral MPA was either combined sequentially at 10 mg/day[16,20] or continuously at 2.5 mg/day[16,20]. In all studies, mean fasting serum glucose was within the normal range at baseline[15,16,20]. All three studies showing an impact of combined MHT on serum glucose levels reported a significantly beneficial decrease of fasting glucose levels by MHT[15,16,20] compared to placebo[16,20]. Within-group comparisons did not reveal a significant difference between active treatment arms (estrogens alone vs. estrogens combined with MPA or MP, sequentially vs. continuously combined MHT containing MPA)[16]. However, 2-h glucose levels (after glucose challenge per oral glucose tolerance test) were significantly higher in all active treatment arms compared to placebo[16,20], without significant group differences between treatment arms in one study[16] and higher 2-h glucose level in women treated with combined MHT containing MPA (sequential and continuous)[20]. Women with increased serum 1-h glucose or fasting insulin level at baseline had the greatest MHT benefit on glucose metabolism[16]. The studies showing no impact on fasting glucose levels were either prospective observational cohort studies[17,18,23], a randomized head-to-head trial[6], or cross-over randomized trials[13,21,23]. The cohort sizes ranged from 20[20] to 86[6,13] postmenopausal women. Study duration was from 3 months[6] to 1 year[17,18,23]. MHT contained either oral[13,16,21–23], transdermal[6,13,21], or nasal[6,21] estrogens at a standard dose[6,13,17,18,21–23] or low dose[13,22]. MP was combined sequentially[6,13,17,18,21–23]. The route of application was either oral at 100 mg/day[17,23] or 300 mg/day[21], or vaginal at 100 mg/day[18] or 200 mg/day[6,13,22]. DRSP[22] at 2 mg/day was taken orally and continuously combined. At study baseline, mean fasting glucose levels were within the normal range in five studies[6,13,17,18,22], increased in one study[21], and not known in one study[23].

The impact of MP combined with estrogens on serum fasting insulin levels was assessed in six studies[6,13,16,20–22]. Of those studies, one reported a significant impact on fasting

insulin levels[16] while five did not[6,13,20–22]. The study showing an impact on fasting insulin levels was a PC-RCT comprising 788 postmenopausal women[16]. Study duration was 3 years[16]. MHT contained oral estrogens at a standard dose. Oral MP was given sequentially at 200 mg/day, and oral MPA was given sequentially at 2.5 mg/day or 10 mg/day[16]. At study baseline, mean insulin levels were within the normal range. There was a significant decrease of fasting serum insulin levels after 36 months of MHT but not placebo[16]. Within-group comparisons did not reveal a significant difference between active treatment arms (estrogens alone vs. estrogens combined with MPA or MP, sequentially vs. continuously combined MHT containing MPA). Women with increased serum 1-h glucose or fasting insulin level at baseline had the greatest MHT benefit on glucose metabolism[16]. The five studies showing no impact on fasting serum insulin levels were a randomized head-to-head trial[6] or PC-RCT[20] including three cross-over randomized trials[13,21,22]. The sample size ranged from 21[21] to 875[20] postmenopausal women. Study duration ranged from 3 months[6] to 3 years[20]. MHT contained either oral[13,20–22], transdermal[6,13,21], or nasal[6,13,22] estrogens at a standard dose[6,13,20–22] or low dose[13,22]. MP was applied sequentially[6,13,20–22], by vaginal route (at 200 mg/day[6,13,22] or 600 mg/day[21]), or per os (at 200 mg/day[20] or 300 mg/day[21]). Oral MPA was taken at 2.5 mg/day[20] or 10 mg/day[20], either continuously or sequentially[20]. Oral DRSP was given continuously at 2 mg/day[22]. At study baseline, mean insulin levels were within the normal range in all but one study[21].

The impact of MP combined with estrogens[15,21] on serum insulin resistance, evaluated by HOMA-IR or QUICKI, was assessed in two studies. At study baseline, mean insulin resistance was either absent[15] or present[21] (HOMA-IR 3.5–3.8). In detail, studies assessing serum insulin resistance were either a prospective observational cohort study[15] or a cross-over randomized trial[21]. Sample sizes ranged from 21[21] to 58[15] postmenopausal women. Study duration was up to 3 years[15]. MHT contained either transdermal[15,21] or oral[21] estrogens at a standard dose[21] or ultralow dose[15]. MP was combined either continuously[15] or sequentially[21]. Route of application was either transdermal[15] at 20–60 mg/day or oral[21] at 300 mg/day. Combined MHT containing MP and MP alone did not change insulin resistance[15,21]. Studies assessing serum HbA1C change were either a PC-RCT[14] or cross-over randomized trial[21], comprising between 21[21] and 25[14] postmenopausal diabetic women. Study duration was from 6 months[14] to 16 months[21]. MHT contained either transdermal[14,21] or oral estrogens[21] at a standard dose. MP was combined sequentially[14,21]. Route of application was oral at 200 mg/day[14] or 300 mg/day[21]. At study baseline, mean HbA1c was within the normal range[21] or increased (>7%)[14]. Neither study reported a significant change in HbA1c. There were no studies comparing MHT containing different progestogens.

Discussion

Ageing is accompanied by a change in body composition such as a decrease of subcutaneous fat tissue, an increase of visceral fat tissue, and a decrease of muscle mass. As muscle mass has a higher metabolic rate than fat tissue, loss of muscle mass leads to a decrease in energy expenditure. Furthermore, central obesity results in several adverse metabolic consequences including dysglycemia, dyslipidemia, hypertension, and cardiovascular disease[24]. The decrease of estrogens during menopause aggravates this effect by increasing food intake and decreasing brown fat activity and body temperature, resulting in a decreased energy expenditure and increasing central fat tissue accumulation, respectively. In addition, the decrease of progesterone production has been found to enhance central fat tissue accumulation as it usually opposes cortisol action[25]. Thus, the question arises of whether MHT may counteract at least some of those negative metabolic effects.

According to our systemic literature review including 18 trials, estrogens combined with MP (1) either did not change (eight studies) or reduced (two studies) body weight in normal weight postmenopausal women, (2) had no impact on BMI (seven studies) in normal and overweight postmenopausal women, (3) do not change (eight studies) or improve (three studies; regardless of MHT regimen) fasting serum glucose levels in (non-)diabetic postmenopausal women, (4) do not change (seven studies) or improve (two studies) fasting serum insulin levels in (non-)diabetic postmenopausal women, (5) do not change insulin resistance regardless of whether insulin resistance was present at baseline or not (two studies), and (6) have no impact on serum HbA1c in postmenopausal diabetic women regardless of their medical treatment for serum glucose control.

Estrogens have been shown to have a beneficial impact on body weight via several influencing factors[4]. In addition, theoretically, MP containing MHT also could have a positive impact on body weight in menopausal women by its diuretic properties[26] increasing the body core temperature[27], increasing serum free thyroxin levels[28], and supporting sleep and thereby the growth hormone peak while sleeping[29]. However, in this systematic review, only three studies[8,10,11] found a change in body weight while the remainder did not observe any change. Accordingly, BMI was generally not affected but remained stable. In those studies that observed a change in body weight, the direction was beneficial showing either a weight reduction or less weight gain with estrogens combined with MP compared to placebo. There are several possible reasons for why only three studies[8,10,11] found a reduction in body weight. The study designs, cohort characteristics, cohort sizes, glucose metabolism assessment methods, and especially treatment regimens and duration differed tremendously. When starting MHT, estrogens may induce an initial fluid retention increasing body weight by 1–2 kg[30,31], which might mask the potential long-term benefit of estrogens and MP on body weight. Thus, a minimum of several weeks or months of treatment might be necessary to measure a difference. As most studies used combined MHT and not MP alone it remains unclear whether weight reduction and weight stabilization is preferably due to estrogens or whether MP has a supporting impact or not. As one of the biggest PC-RCTs[10] found a significant difference between all active treatment arms and placebo but not between active treatment arms, we speculate that estrogens may play the more important role in regulating body weight.

Indeed, three studies[10,16,20] had a group of women taking unopposed CEE. Two of these studies[10,16] reported no significant difference between estrogens alone and opposed estrogens in terms of changes in body weight, glucose, or insulin metabolism. We can therefore deduce that those changes are mainly due to estrogens and not to MP. The third study[20] also reported no significant difference between unopposed and opposed estrogens concerning glucose metabolism. A significant change in body weight was found only between placebo and unopposed CEE, which reinforces the statement that the changes are mainly due to estrogens. Route of estrogen administration may also have an impact on body weight and glucose metabolism. Studies included in our review mainly contained either oral (seven studies) or transdermal (eight studies) estrogens but rarely nasal estrogens (three studies). There is some evidence that weight gain is lower when estrogens are applied transdermally[32]. According to our systematic review, MHT containing MP did not change or improved fasting serum glucose, insulin, and insulin resistance in (non-)diabetic women. This finding supports various international guidelines on MHT reporting a decreased risk for developing type 2 diabetes mellitus in non-diabetic postmenopausal women due to any MHT (e.g. North American Menopause Society[33], National Institute for Health and Care Excellence[34], International Menopause Society[35], European Menopause and Andropause Society[36]). Similarly, in diabetic women, MHT containing MP did not alter serum HbA1c levels[14,21], which is also in line with, for example, the National Institute for Health and Care Excellence guideline[34]. Interestingly, in some studies using an oral glucose tolerance test[16,20] the 2-h serum glucose was increased by MHT, which seems to contradict the glucose decreasing effect of estrogens. However, this finding might be due to an estrogen-induced decrease of insulin secretion[15] and/or enhanced hepatic insulin clearance[15]. Accordingly, in a fasting state estrogens may reduce fasting serum glucose levels by inhibiting gluconeogenesis[37]. After a glucose challenge test, serum glucose levels increase and may not be as quickly lowered as available insulin levels are diminished by estrogens.

Our systematic review also has limitations. Importantly, the studies identified were very heterogeneous and mostly used combined MHT, making a clear conclusion for MP difficult. Also, we were not able to identify a subgroup of postmenopausal women who responded with weight loss due to MHT or MP, respectively. As we only included studies on postmenopausal women, we cannot extend our conclusion to premenopausal or perimenopausal women using MHT or MP for other reasons. The studies included in our review either applied MP orally or vaginally, which may lead to different serum levels[38]. Taken together with the different MP dosages applied for varying durations of time we were not able to identify a certain minimum MP dosage and treatment duration plus preferable regimen (sequential vs. continuous) and route of application (oral vs. vaginal) that would be specifically recommendable. Some studies also applied synthetic progestogens that have different metabolic properties than MP. For example, bioavailability differs between progestogens, being more than 90% for MPA, chlormadinone acetate, and trimegestone and less than 5% for MP[39]. Taken together, most studies did not show an impact on the parameters under examination. However, none of the studies reported a negative impact of MHT on body weight, BMI, and glucose metabolism. Thus, postmenopausal women can be reassured that MHT has a neutral or even beneficial effect on body weight. However, when discussing the pros and cons of MHT with patients, the type of estrogen and progestogen also needs to be addressed. For example, MP displays anti-androgenic and anti-mineralocorticoid properties which may counteract signs of hyperandrogenism and fluid retention, respectively, often associated with menopause[40]. Furthermore, MP decreases menopausal vasomotor symptoms[41] and, via its metabolite allopregnanolone, supports sleep and may reduce anxiety[42]. In the long term, MHT containing MP seems to have fewer adverse effects on the mammary gland[43] and cardiovascular system[44,45] when compared to MHT containing synthetic progestogens.

Conclusion

According to our systematic review on MHT containing bioidentical MP in postmenopausal women, estrogens combined with MP have no impact on BMI or may even reduce body weight and display a neutral or beneficial effect on glucose metabolism. This beneficial effect is probably mostly due to the estrogen MHT component. In respect to the progestogen component, MP displays a better glucose metabolism profile than MPA. When MHT is indicated we can therefore recommend choosing MHT containing MP as it improves or at least stabilizes postmenopausal glucose profiles. MHT may also be recommended in diabetic postmenopausal women given that fasting serum glucose is improved and insulin reduced. In any case, postmenopausal women and their physicians can be reassured that MHT containing MP does not adversely affect body weight or glucose metabolism and has some additional benefits when compared to MHT containing synthetic progestogens.

Acknowledgement

The authors are grateful for the support of DR. KADE/BESINS Pharma GmbH in helping with ordering the identified publications.

Conflict of interest P. Stute has been part of a German-speaking expert board funded by DR. KADE/BESINS Pharma GmbH. A. Coquoz and C. Gruetter do not have any conflict of interest. The authors alone are responsible for the content and writing of the article.

Source of funding This publication was not funded.

References

1. Csapo AI, Pulkkinen M. Indispensability of the human corpus luteum in the maintenance of early pregnancy. Luteectomy evidence. *Obstet Gynecol Surv* 1978;33:69–81
2. de Villiers TJ, Pines A, Panay N, *et al.* Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2013;16:316–37
3. Davis SR, Castelo-Branco C, Chedraui P, *et al.* Understanding weight gain at menopause. *Climacteric* 2012;15:419–29

4. Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. *Endocr Rev* 2013;34:309–38
5. Birkhauser MH, Panay N, Archer DF, *et al.* Updated practical recommendations for hormone replacement therapy in the peri- and postmenopause. *Climacteric* 2008;11:108–23
6. Casanova G, Spritzer PM. Effects of micronized progesterone added to non-oral estradiol on lipids and cardiovascular risk factors in early postmenopause: a clinical trial. *Lipids Health Dis* 2012; 11:133
7. Hassager C, Christiansen C. Estrogen/gestagen therapy changes soft tissue body composition in postmenopausal women. *Metab Clin Exp* 1989;38:662–5
8. Cicinelli E, de Ziegler D, Alfonso R, *et al.* Endometrial effects, bleeding control, and compliance with a new postmenopausal hormone therapy regimen based on transdermal estradiol gel and every-other-day vaginal progesterone in capsules: a 3-year pilot study. *Fertil Steril* 2005;83:1859–63
9. Di Carlo C, Tommaselli GA, Gargano V, *et al.* Transdermal estradiol and oral or vaginal natural progesterone: bleeding patterns. *Climacteric* 2010;13:442–6
10. Espeland MA, Stefanick ML, Kritz-Silverstein D, *et al.* Effect of postmenopausal hormone therapy on body weight and waist and hip girths. Postmenopausal Estrogen-Progestin Interventions Study Investigators. *J Clin Endocrinol Metab* 1997;82:1549–56
11. Cicinelli E, de Ziegler D, Galantino P, *et al.* Twice-weekly transdermal estradiol and vaginal progesterone as continuous combined hormone replacement therapy in postmenopausal women: a 1-year prospective study. *Am J Obstet Gynecol* 2002;187:556–60
12. Di Carlo C, Sammartino A, Di Spiezio Sardo A, *et al.* Bleeding patterns during continuous estradiol with different sequential progestogens therapy. *Menopause* 2005;12:520–5
13. Casanova G, dos Reis AM, Spritzer PM. Low-dose oral or non-oral hormone therapy: effects on C-reactive protein and atrial natriuretic peptide in menopause. *Climacteric* 2015;18:86–93
14. Mosnier-Pudar H, Faguer B, Guyenne TT, Tchobroutsky G. [Effects of deprivation and replacement by percutaneous 17 beta estradiol and oral progesterone on blood pressure and metabolic parameters in menopause patients with non-insulin-dependent diabetes]. *Arch Mal Coeur Vaiss* 1991;84:1111–5
15. Stephenson K, Neuenschwander PF, Kurdowska AK. The effects of compounded bioidentical transdermal hormone therapy on hemostatic, inflammatory, immune factors; cardiovascular biomarkers; quality-of-life measures; and health outcomes in perimenopausal and postmenopausal women. *Int J Pharm Compd* 2013;17:74–85
16. Espeland MA, Hogan PE, Fineberg SE, *et al.* Effect of postmenopausal hormone therapy on glucose and insulin concentrations. PEPI Investigators. Postmenopausal Estrogen/Progestin Interventions. *Diabetes Care* 1998;21:1589–95
17. Bolaji II, Grimes H, Mortimer G, *et al.* Low-dose progesterone therapy in oestrogenised postmenopausal women: effects on plasma lipids, lipoproteins and liver function parameters. *Eur J Obstet Gynecol Reprod Biol* 1993;48:61–8
18. Spritzer PM, Vitola D, Vilodre LC, *et al.* One year follow-up of hormone replacement therapy with percutaneous estradiol and low-dose vaginal natural progesterone in women with mild to moderate hypertension. *Exp Clin Endocrinol Diabetes* 2003;111:267–73
19. Darj E, Nilsson S, Axelsson O, Hellberg D. Clinical and endometrial effects of oestradiol and progesterone in post-menopausal women. *Maturitas* 1991;13:109–15
20. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA* 1995;273:199–208
21. Araujo DA, Farias ML, Andrade AT. Effects of transdermal and oral estrogen replacement on lipids and glucose metabolism in postmenopausal women with type 2 diabetes mellitus. *Climacteric* 2002;5:286–92
22. Casanova G, Radavelli S, Lhullier F, Spritzer PM. Effects of nonoral estradiol-micronized progesterone or low-dose oral estradiol-drospirenone therapy on metabolic variables and markers of endothelial function in early postmenopause. *Fertil Steril* 2009;92:605–12
23. Bolaji II, Mortimer G, Grimes H, *et al.* Clinical evaluation of near-continuous oral micronized progesterone therapy in estrogenized postmenopausal women. *Gynecol Endocrinol* 1996;10:41–7
24. Kapoor E, Collazo-Clavell ML, Faubion SS. Weight gain in women at midlife: a concise review of the pathophysiology and strategies for management. *Mayo Clin Proc* 2017;92:1552–8
25. Gonzalez-Garcia I, Tena-Sempere M, Lopez M. Estradiol regulation of brown adipose tissue thermogenesis. *Adv Exp Med Biol* 2017; 1043:315–35
26. Regidor P-A. Progesterone in peri- and postmenopause: a review. *Geburtshilfe Frauenheilkd* 2014;74:995–1002
27. Cagnacci A, Volpe A, Paoletti AM, Melis GB. Regulation of the 24-hour rhythm of body temperature in menstrual cycles with spontaneous and gonadotropin-induced ovulation. *Fertil Steril* 1997;68: 421–5
28. Caufriez A, Leproult R, L'Hermite-Baleriaux M, Kerkhofs M, Copinschi G. Progesterone prevents sleep disturbances and modulates GH, TSH, and melatonin secretion in postmenopausal women. *J Clin Endocrinol Metab* 2011;96:E614–23
29. Copinschi G, Caufriez A. Sleep and hormonal changes in aging. *Endocrinol Metab Clin North Am* 2013;42:371–89
30. Burkman RT, Fisher AC, LaGuardia KD. Effects of low-dose oral contraceptives on body weight: results of a randomized study of up to 13 cycles of use. *J Reprod Med* 2007;52:1030–4
31. Oelkers W. The renin-aldosterone system and drospirenone. *Gynecol Endocrinol* 2002;16:83–7
32. Goodman MP. Are all estrogens created equal? A review of oral vs. transdermal therapy. *J Womens Health (Larchmt)* 2012;21:161–9
33. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The hormone therapy position statement of The North American Menopause Society. *Menopause* 2017;24:728–53
34. Sarri G, Davies M, Lumsden MA, Guideline Development Group. Diagnosis and management of menopause: summary of NICE guidance. *BMJ* 2015;351:5746
35. Baber RJ, Panay N, Fenton A, IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. *Climacteric* 2016;19:109–50
36. Armeni E, Lambrinoudaki I, Ceausu I, *et al.* Maintaining postreproductive health: a care pathway from the European Menopause and Andropause Society (EMAS). *Maturitas* 2016;89:63–72
37. Washburn BS, Krantz JS, Avery EH, Freedland RA. Effects of estrogen on gluconeogenesis and related parameters in male rainbow trout. *Am J Physiol* 1993;264:R720–5
38. Ruan X, Mueck AO. Systemic progesterone therapy-oral, vaginal, injections and even transdermal? *Maturitas* 2014;79:248–55
39. Stanczyk FZ, Hapgood JP, Winer S, Mishell DR. Jr., Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects. *Endocr Rev* 2013;34:171–208
40. Kuhl H. Pharmacology of Progestogens. *J Reproduktionsmed Endokrinol* 2011;8:157–77
41. Prior JC. Progesterone for treatment of symptomatic menopausal women. *Climacteric* 2018;21:358–65
42. Schumacher M, Mattern C, Ghoumari A, *et al.* Revisiting the roles of progesterone and allopregnanolone in the nervous system: resurgence of the progesterone receptors. *Prog Neurobiol* 2014; 113:6–39
43. Stute P, Neulen J, Wildt L. The impact of micronized progesterone on breast cancer risk: a systematic review. *Climacteric* 2018;21:111–22
44. Canonico M, Carcaillon L, Plu-Bureau G, *et al.* Postmenopausal hormone therapy and risk of stroke: impact of the route of estrogen administration and type of progestogen. *Stroke* 2016;47:1734–41
45. Canonico M, Fournier A, Carcaillon L, *et al.* Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol* 2010;30:340–5