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ORIGINAL STUDY

Weight loss response to semaglutide in postmenopausal women with and without hormone therapy use

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Abstract

Objective: To compare weight loss response and changes in cardiometabolic risk markers in postmenopausal women using semaglutide with and without menopause hormone therapy (HT) use.

Methods: Retrospective cohort study of postmenopausal women treated with semaglutide for overweight or obesity for ≥3 months. Endpoints: total body weight loss percentage (TBWL%) at 3, 6, 9, and 12 months after semaglutide initiation; and percentage of women achieving ≥5% and ≥10% TBWL and changes in cardiometabolic risk markers (glucose, blood pressure, and lipids) at 12 months.

Results: There were 16 women on HT and 90 on no-HT; mean age 56 ± 8 vs 59 ± 8 yr, $P = 0.2$ and mean BMI 36 ± 5 vs 39 ± 8 kg/m^2, $P = 0.1$; respectively. Among women on no-HT, White race, dyslipidemia, and depression were more prevalent. Women on HT had a higher TBWL% at 3, 6, 9, and 12 months: 7 ± 3% vs 5 ± 4%, $P = 0.01$; 13 ± 6% vs 9 ± 5%, $P = 0.01$; 15 ± 6% vs 10 ± 6%, $P = 0.02$; and 16 ± 6% vs 12 ± 8%, $P = 0.04$; respectively. After adjusting for potential confounders, this association remained significant across time. At 12 months, a greater percentage of women on HT achieved ≥5% and ≥10% TBWL. Both groups experienced an improvement in cardiometabolic risk markers.

Conclusion: In postmenopausal women with overweight or obesity treated with semaglutide, HT use was associated with an improved weight loss response. This association was maintained when adjusted for confounders. Larger studies should be conducted to confirm these results.

Key Words: Antiobesity medications – Hormone therapy – Menopause – Obesity – Semaglutide.

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During the menopause transition, up to 70% of women experience weight gain.[1] Weight gain is typically modest and estimated at 2.1 kg.[2-5] While aging and estrogen decline play a key role, additional factors have also been identified.[6,7] For instance, through the menopause transition, women experience a decrease in total 24-hour energy expenditure by 9% and a decrease in spontaneous physical activity energy expenditure by 30%.[8] Aside from weight gain, the menopause transition is associated with changes in body composition including an increase in fat mass, a decrease in lean mass, and an increase in abdominal adiposity.[8,9] These changes in weight and body composition increase the risk for cardiometabolic diseases, as evidenced by the increased prevalence of type 2 diabetes, dyslipidemia, metabolic dysfunction-associated steatotic liver disease (MASLD-previously referred to as nonalcoholic fatty liver disease), and cardiovascular disease (CVD) after menopause.[10-14]

There is evidence that use of menopause hormone therapy (HT) can partially mitigate these changes. During menopause, HT use, compared to no-HT use, has been shown to attenuate the increase in total and visceral abdominal adiposity by around 60% and to decrease waist circumference and body mass index (BMI) by 0.8%.[9,15,19] HT use has not only been associated with the attenuation of lean mass loss but with an increase in lean mass by 1%.[15,20] Furthermore, HT use decreases vasomotor symptoms during the menopause transition which can lead to improved sleep, increased activity, and overall increased quality of life, all factors that can further mitigate the changes in body composition experienced during menopause.[21] Additional favorable effects of HT use include an improvement in glucose metabolism, a reduction in the risk of diabetes, an improvement in the lipid profile, a decrease in the incidence of MASLD, and an overall favorable impact on CVD risk.[10,16,18,22]

Weight loss can improve cardiometabolic diseases, consequently decreasing CVD and mortality risks.[23] As CVD is the leading cause of mortality in women and menopause is an independent risk factor for CVD, interventions to prevent weight gain and manage overweight and obesity are of particular importance in postmenopausal women.[24] Semaglutide is a glucagon-like peptide 1 receptor agonist approved for the treatment of overweight and obesity that leads to a mean weight loss of 15% after 68 wk, weight loss that is superior to other antiobesity medications.[25-32] Furthermore, the recent Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes (SELECT) trial reported that semaglutide decreases the risk of major cardiovascular events by 20%, becoming the only antiobesity medication shown to improve cardiovsacular outrcomes in adults with overweight and obesity.[33]

This study compared weight loss response to semaglutide between postmenopausal women with and without HT use. It further determined if cardiometabolic risk markers such as fasting glucose, glycosylated hemoglobin A1c (HbA1c), blood pressure, and lipid profile changed over 12 months of semaglutide use by group. We hypothesized that in postmenopausal women using semaglutide for the treatment of overweight and obesity, HT use would be associated with an improved weight loss response as compared to postmenopausal women without HT use. We further hypothesized that this improvement would result in a more favorable cardiometabolic risk profile.

METHODS

Study design and participants

This study is a retrospective review of the electronic medical records (EMRs) of patients in the Mayo Clinic Health System using semaglutide for the treatment of overweight or obesity (BMI >27 kg/m^2) between January 1, 2021, and March 31, 2023. This study compared weight loss outcomes and changes in cardiometabolic risk markers in response to semaglutide between postmenopausal women with and without systemic HT use (HT vs no-HT). Menopause status was defined as women ≥40 years who had ≥12 months of amenorrhea not related to other causes (eg, use of contraceptives) or women with a history of bilateral oophorectomy. Women older than age 40 years with a history of hysterectomy or endometrial ablation with a documented follicle stimulating hormone (FSH) level greater than 50 IU/L were also included. Women in the no-HT group had to have never received systemic HT. Women were included in the HT group only if HT was started prior to semaglutide initiation and continued throughout the duration of semaglutide treatment. Exclusion criteria included less than 3 months of semaglutide use, history of bariatric surgery, and active malignancy. HT consisted of transdermal or oral estradiol with or without a progestogen based on hysterectomy status. The Mayo Clinic Institutional Review Board (IRB) waived the need for obtaining informed consent from our patients due to minimal risk attributed to this study.

Data collection

Data were collected from the EMRs at baseline (ie, at semaglutide initiation) and at 3, 6, 9, and 12 months after semaglutide initiation. A 30-d range was implemented for each of the time points. Data collected included basic demographic and social characteristics including age, race, ethnicity, marital status, level of education (classified as less than college, i.e., high or middle school; college; and more than college, ie, master and doctoral degrees), and financial situation (self-reported and classified by the existence of financial strain). Additional data collected included anthropometrics (weight, height, and BMI); blood pressure; medical history pertaining to adiposity-related diseases including dyslipidemia, hypertension, type 2 diabetes, gastroesophageal reflux disease, MASLD, and obstructive sleep apnea; mental health history including depression and anxiety; and laboratory data including HbA1c, fasting glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Medication data included semaglutide dosing, which was categorized as low dose (0.25 to 1 mg weekly) and high dose (1.7 to 2.4 mg weekly), and dose and type of systemic HT (ie, transdermal or oral estrogen and progestogen use). Information on the use of weight-promoting medications during the time of semaglutide treatment was also collected. These medications included insulin, sulfonylureas, thiazolidinediones, antipsychotics (olanzapine, clozapine, risperidone, quetiapine, haloperidol, among others), antidepressants (selective serotonin reuptake inhibitors, monoamine oxidase

inhibitors, and tricyclics), antihistamines, anticonvulsants (gabapentin, valproic acid, carbamazepine, among others), β-blockers, and corticosteroids.[34] Age at menopause was collected when reported in the EMR. Furthermore, data on whether patients met with a dietitian or a behavior modification therapist for weight loss, and the number of visits with each provider were also collected.

Study end points

The primary endpoint was the percentage of total body weight loss (TBWL%) at 12 months after semaglutide initiation by HT use. TBWL% was calculated using the formula:

$$100 \times \frac{\text{weight at baseline visit (kg)} - \text{weight at followup visit (kg)}}{\text{weight at baseline visit (kg)}}$$

The secondary endpoints included: TBWL% at 3, 6, and 9 months after semaglutide initiation and percentage of women achieving ≥5%, ≥10%, ≥15%, and ≥20% of TBWL 12 months after semaglutide initiation by HT use. In addition, changes in cardiometabolic risk markers from baseline to 12 months were evaluated including blood pressure, fasting glucose, HbA1c, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. A subgroup analysis of women on high dose of semaglutide (ie, semaglutide 1.7–2.4 mg weekly) was performed for all primary and secondary endpoints.

Statistical analysis

Data analysis was performed using JMP®, Version 16 (SAS Institute Inc., Cary, NC, 1989–2019). Given the normal distribution of variables, continuous data were summarized as mean and standard deviation (mean ± SD). Categorical data were reported as frequencies and percentages. The independent t-test and Pearson χ^2 were used to compare continuous and categorical variables among the two groups, respectively. Paired *t* test was used to compare changes from baseline and 12 months within each group. Multiple regression analyses were performed to adjust TBWL% outcomes for variables that were significantly different between groups at baseline. Similarly, TBWL% outcomes were adjusted for variables known to affect weight loss response to semaglutide, including age, baseline weight, type 2 diabetes at baseline, as well as nutritional and behavioral support. Mixed linear models were used to estimate associations with weight loss across time. A compound symmetric covariance structure was used. For regression analyses, the β-coefficient with 95% confidence interval (CI) were reported. All two-tailed *P* values <0.05 were considered statistically significant. The Strengthening

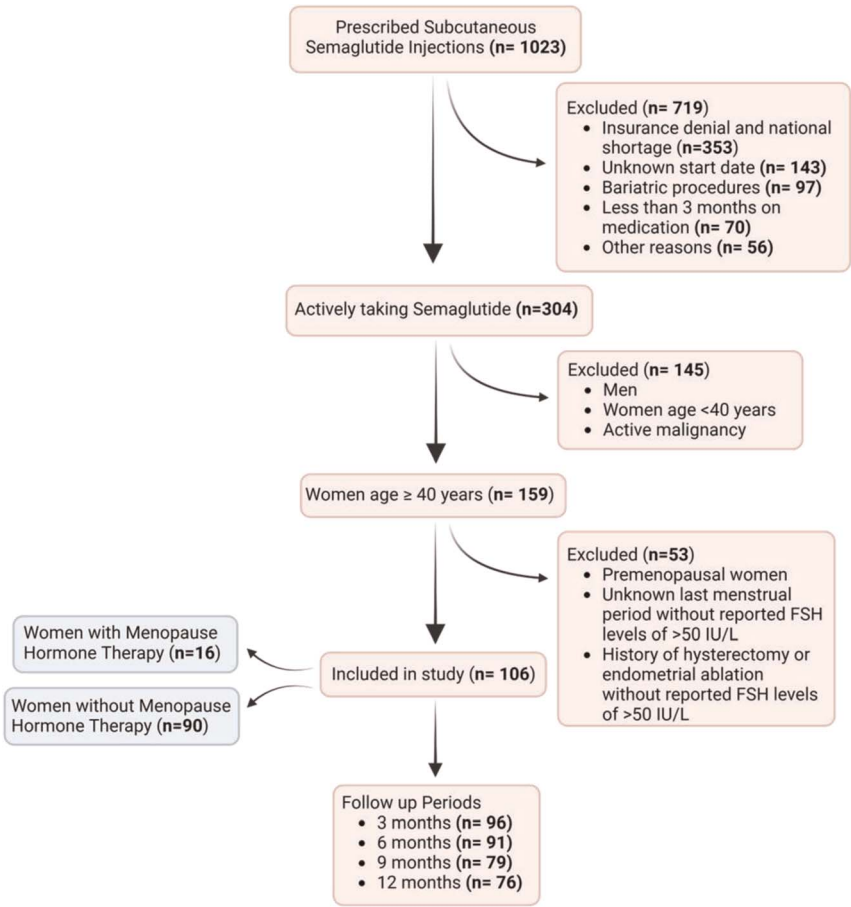


FIG. 1. Study flowchart. FSH, follicle-stimulating hormone.

the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline were followed.

RESULTS

A total of 1,023 patients from the Mayo Clinic Health System were prescribed semaglutide injections for weight loss between January 2021 and March 2023. Seven-hundred nineteen patients (70%) were excluded due to prescription insurance denial, inability to use the medication due to the national shortage in 2021 and 2022, and less than 3 months of medication use. From the 304 patients taking semaglutide for the treatment of overweight or obesity, 82 (27%) were men and 63 (21%) were women younger than 40 years and were therefore excluded. All women ≥40 years, 159 women, were screened for menopause status and current HT use. From these, 53 (33%) were excluded as they were premenopausal, their last menstrual period was unknown with no documented FSH levels, or because they had a hysterectomy with no documented FSH levels. Figure 1 summarizes the process for patient selection.

Baseline characteristics

There was a total of 106 postmenopausal women taking semaglutide for the treatment of overweight or obesity. The cohort was mostly comprised of White, married, college-educated women in their late 50s with an average BMI in the obesity category class II (Table 1). Most of our cohort was not on HT (n = 90 vs n = 16 for HT). There were no differences in age, weight, BMI, or type of menopause (natural vs surgical) among the two groups (Table 1). White race was more prevalent in women in the no-HT group compared to HT group (93% vs 75%, $P = 0.04$). There were no differences in ethnicity, marital status, level of education, or financial strain among the two groups.

In women using systemic HT, 50% used transdermal estradiol at variable doses between 0.025 to 0.1 mg/d. The other half received oral estradiol between 0.5 and 1 mg daily. Six women (38%) were concomitantly using 100 mg of oral progesterone daily. More women using HT achieved a high dose of semaglutide (1.7–2.4 mg/weekly), although this difference did not reach statistical significance (88% vs 66%, $P = 0.06$; Table 1). In those women achieving a high dose of semaglutide, there were no differences in any of the baseline demographic, social, and anthropometric characteristics among HT and no-HT use (Supplemental Table 1, http://links.lww.com/MENO/B220). Among the entire cohort, 14% were using weight-promoting medications at the same time of semaglutide use. There were no differences in the prevalence of weight-promoting medication use among the two groups (Table 1).

The prevalence of adiposity-related diseases varied among the two groups. In women using HT, the most common adiposity-related diseases were hypertension (44%), followed by gastroesophageal reflux disease (38%) and dyslipidemia (25%). In women on no-HT, the most common adiposity-related diseases were dyslipidemia (68%), followed by hypertension (62%) and obstructive sleep apnea (43%). While the prevalence of adiposity-related diseases varied among the two groups, the differences were not statistically significant except for dyslipidemia and

TABLE 1. *Baseline demographic, social, and clinical characteristics of the cohort by HT use (n = 106)*

	All Cohort N = 106	HT n = 16	no-HT n = 90	*P*
Demographic and Social Characteristics				
Age, years	58.4 ± 7.5	56.2 ± 7.6	58.9 ± 7.5	0.2
Race				**0.04**
White (%)	96 (91%)	12 (75%)	84 (93%)	
African American (%)	5 (5%)	1 (6%)	4 (4%)	
Asian Indian	3 (3%)	2 (12%)	1 (1%)	
Asian Japanese	1 (1%)	0 (0%)	1 (1%)	
Ethnicity, Not Hispanic or Latino	102 (96%)	15 (94%)	87 (97%)	0.3
Marital Status				0.1
Married (%)	77 (73%)	14 (87%)	63 (70%)	
Divorced (%)	13 (12%)	2 (13%)	11 (12%)	
Single (%)	12 (11%)	0 (0%)	12 (13%)	
Widowed (%)	4 (4%)	0 (0%)	4 (5%)	
Level of Education				0.4
Less than College	19 (19%)	1 (6%)	18 (21%)	
College	40 (39%)	7 (47%)	33 (38%)	
More than College	43 (42%)	7 (47%)	36 (41%)	
Financial Strain, No	74 (90%)	11 (100%)	63 (89%)	0.12
Baseline Body Composition				
Weight, kg	104.6 ± 20.2	98.3 ± 16.1	105.9 ± 20.6	0.1
BMI, kg/m^2	38.5 ± 7.5	36.4 ± 5.1	38.9 ± 7.8	0.1
Obesity category				0.15
Overweight (≥25 kg/m^2)	8 (8%)	0 (0%)	8 (9%)	
Obesity class I (≥30 kg/m^2)	32 (30%)	8 (50%)	24 (27%)	
Obesity class II (≥35 kg/m^2)	30 (28%)	4 (25%)	26 (29%)	
Obesity class III (≥40 kg/m^2)	36 (34%)	4 (25%)	32 (36%)	
Adiposity-related diseases				
Dyslipidemia	65 (61%)	4 (25%)	61 (68%)	**0.001**
Hypertension	63 (59%)	7 (44%)	56 (62%)	0.2
Gastroesophageal reflux disease	43 (41%)	6 (38%)	37 (41%)	0.8
Obstructive sleep apnea	42 (40%)	3 (19%)	39 (43%)	0.053
Depression	35 (33%)	2 (13%)	33 (38%)	**0.04**
Type 2 diabetes	30 (28%)	2 (13%)	28 (31%)	0.1
Anxiety	27 (26%)	4 (25%)	23 (26%)	0.9
Nonalcoholic fatty liver disease	15 (14%)	1 (6%)	14 (16%)	0.3
Antiobesity medication dosing				0.06
0.25 to 1 mg weekly SQ	33 (31%)	2 (13%)	31 (34%)	
1.7 to 2.4 mg weekly SQ	73 (69%)	14 (88%)	59 (66%)	
Weight-promoting medications				
Concomitant use of weight-promoting medications, yes	15 (14%)	2 (13%)	13 (14%)	0.8
Use of more than one weight-promoting medication, yes	1/15 (7%)	0/2	1/13 (5%)	0.6
Weight management components				
Dietitian visit				
Yes	25 (24%)	4 (25%)	21 (23%)	0.9
No. visits (median, IQ)	1 (1–2.5)	1.5 (1–2)	1 (1–3.5)	0.1
Behavioral therapy				
Yes	12 (11%)	2 (13%)	10 (11%)	0.9
No. visits (median, IQ)	0 (0–3.75)	0.5 (0–1.75)	0 (0–4)	0.07
Menopause				
Natural (vs surgical)	82 (77%)	10 (62%)	72 (80%)	0.15
Type of HT				
Estrogen delivery				
Transdermal	NA	8 (50%)	NA	
Oral		8 (50%)		
Progestogen use				
Yes	NA	6 (38%)	NA	

HT, with hormone therapy; IQ, interquartile range; no-HT, without hormone therapy; SD, standard deviation; SQ, subcutaneous.
Continuous data are summarized asmean ± SD, unless noted otherwise. Categorical data are summarized as frequency and percentage.
All *P* values <0.05 are considered significant.
The bold numbers signify significance, $P < 0.05$.

depression which were more prevalent in women on no-HT. In women achieving a high dose of semaglutide, only dyslipidemia was more prevalent among no-HT users compared to HT users: 64% vs 27%, $P = 0.008$ (Supplemental Table 1, http://links.lww.com/MENO/B220).

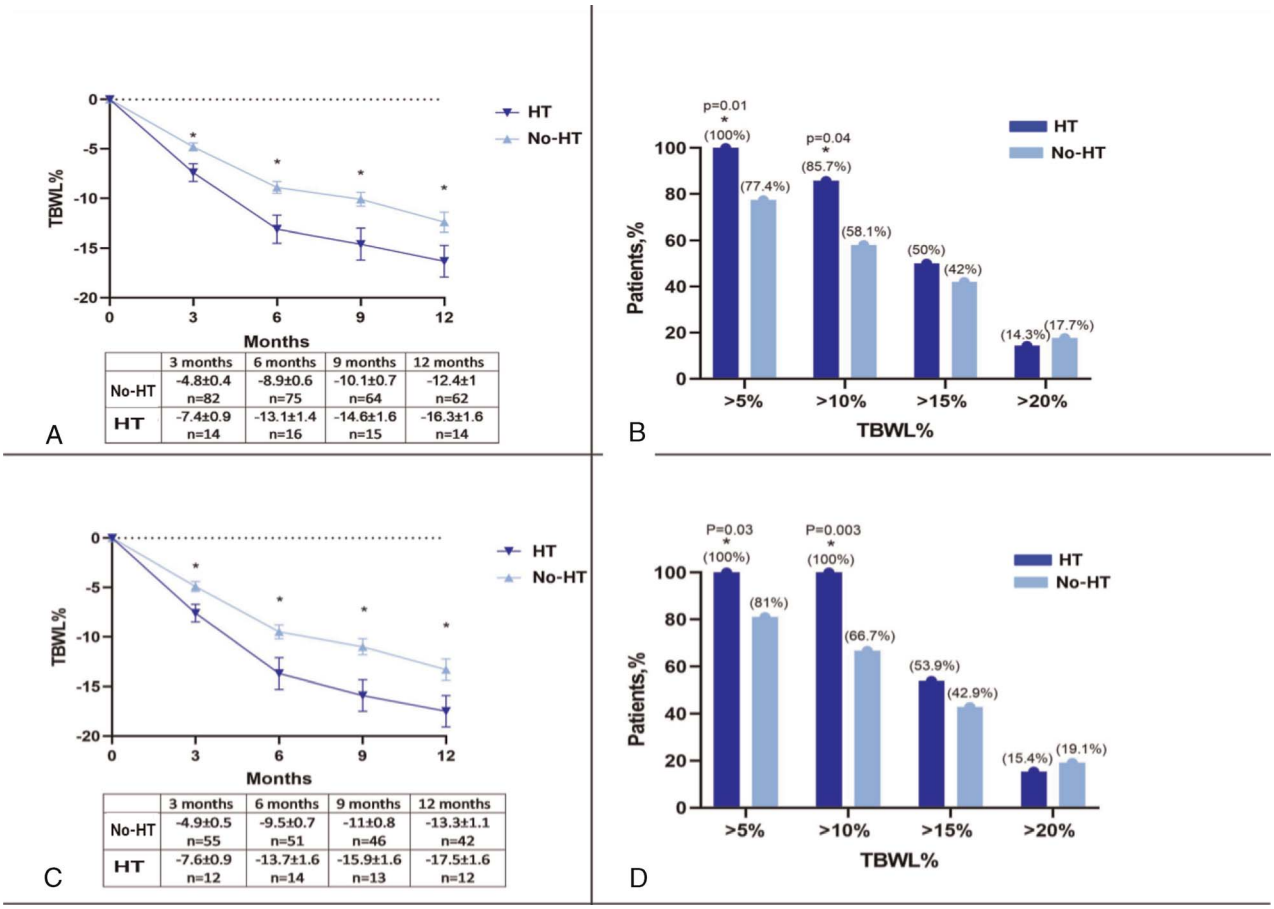
Nutrition and behavioral support were offered to all women as part of the comprehensive weight management program; however, only 25% and 23% of women elected nutritional support in the HT and no-HT groups, respectively; and 13% and 11% elected behavioral support in the HT and no-HT groups, respectively. There were no differences in nutritional and behavioral support among the two groups.

Total body weight loss outcomes

When compared to the no-HT use, women on HT achieved greater TBWL% at 3, 6, 9, and 12 months: 7 ± 3% vs 5 ± 4% (mean difference 2%, $P = 0.01$), 13 ± 6% vs 9 ± 5% (mean difference 4%, $P = 0.01$), 15 ± 6% vs 10 ± 6% (mean difference 5%, $P = 0.02$), 16 ± 6% vs 12 ± 8% (mean difference 4%, $P = 0.04$), respectively (Fig. 2A). Similarly, compared to no-HT use, a higher proportion of women using HT achieved TBWL ≥5% and ≥10% at 12 months, respectively (Fig. 2B). There was no significant difference in the proportion of women achieving categorical TBWL ≥15% and ≥20% between the two groups at 12 months.

When TBWL% was adjusted for semaglutide dose intensity (high [1.7–2.4 mg weekly] vs low [0.25–1 mg weekly]), the differences persisted. Furthermore, in the subgroup analysis of women on a high dose of semaglutide, the differences among the two groups in TBWL% at all timepoints, and the differences in the proportion of women achieving ≥5 and ≥10% TBWL at 12 months also persisted (Fig. 2C and 2D). No differences in weight loss response to semaglutide among postmenopausal women with oral vs transdermal estrogen delivery, or with or without concomitant progesterone use were observed (Supplemental Figs. 1A and B, http://links.lww.com/MENO/B221).

Multiple regression analyses taking into consideration weight loss across all timepoints were performed to account for variables that were statistically different at baseline, including race and the presence of dyslipidemia and depression (Table 2, Model 1A). In this mode, HT use was an independent predictor of TBWL %. A separate multiple regression model took into consideration known variables that affect weight loss response to antiobesity



A	3 months	6 months	9 months	12 months
No-HT	-4.8±0.4 n=82	-8.9±0.6 n=75	-10.1±0.7 n=64	-12.4±1 n=62
HT	-7.4±0.9 n=14	-13.1±1.4 n=16	-14.6±1.6 n=15	-16.3±1.6 n=14

C	3 months	6 months	9 months	12 months
No-HT	-4.9±0.5 n=55	-9.5±0.7 n=51	-11±0.8 n=46	-13.3±1.1 n=42
HT	-7.6±0.9 n=12	-13.7±1.6 n=14	-15.9±1.6 n=13	-17.5±1.6 n=12

FIG. 2. (**A**) Total body weight loss (TBWL) at 3, 6, 9, and 12 months by hormone therapy (HT) use in all women (n = 106); (**B**) Percentage of women achieving ≥5%, ≥10%, ≥15%, and ≥20% of TBWL at 12 months by HT use in all women (n = 106); (**C**) TBWL at 3, 6, 9, and 12 months by HT use in women on high dose [a] of semaglutide (n = 73); (**D**) Percentage of women on high dose [a] of semaglutide achieving ≥5%, ≥10%, ≥15%, and ≥20% of TBWL at 12 mo by HT use (n = 73). HT, with hormone therapy; no-HT, without hormone therapy; TBWL, total body weight loss. All *P* values <0.05 are considered significant. Data in the figures are presented as mean ± standard error of the mean. [a]High dose of semaglutide was defined as a dose of 1.7 to 2.4 mg weekly. *$P < 0.05$.

medications including age, baseline weight, type 2 diabetes, and nutritional and behavioral support (Table 2, Model 2A). In this model, HT use also predicted TBWL% with significance. Similar results of these two models were also observed in the subgroup analysis of women taking high doses of semaglutide with or without HT use (Table 2, Models 1B and 2B).

Changes in Cardiometabolic risk markers

Both groups had improvement in cardiometabolic risk markers (Fig. 3 and Supplemental Table 2, http://links.lww.com/MENO/B220). Women on no-HT had a significant improvement in fasting glucose, HbA1c, and systolic blood pressure. Women on HT had significant improvement in HbA1c, triglycerides, and total cholesterol. For these women, there was a near significant improvement in systolic blood pressure and LDL-cholesterol ($P = 0.06$ for both). In the women on high doses of semaglutide, women on no-HT had a significant improvement in HbA1c and systolic blood pressure and women on HT had a significant improvement in HbA1c, triglycerides, and total cholesterol, with a trend toward improvement in systolic blood pressure and LDL-cholesterol (Supplemental Table 3, http://links.lww.com/MENO/B220). We compared the changes from baseline to 12 months of each cardiometabolic risk marker among the two groups and no differences were observed (data not shown).

DISCUSSION

In this study, the weight loss response to semaglutide differed between postmenopausal women with and without HT use. Three, 6, 9, and 12 months after semaglutide initiation, HT use was associated with approximately 30% more weight loss. After adjusting for potential confounding variables this association remained significant across time. Similarly, at 12 months, HT use was associated with a greater probability of achieving ≥5% and ≥10% TBWL. The weight loss observed in our study was associated with an improvement in cardiometabolic risk markers, regardless of HT use.

These results replicate the effectiveness of semaglutide in phase 3 clinical trials and real-world studies.[26,28] The 16% total body weight loss observed in the HT group, is similar to the weight loss response to semaglutide in pivotal studies.[25,26] We observed an inferior weight loss response in the no-HT group that cannot be explained by the presence of factors that can affect weight loss, such as age, baseline weight, the presence of type 2 diabetes at baseline, and semaglutide dosage. Given the retrospective nature of the study, we were unable to identify factors other than HT use that could explain this differential response.

While the difference in weight loss response among the two groups may be explained by the positive effects of HT on body composition changes, other factors need to be considered.[9,15] The primary indication for HT is for the treatment of vasomotor symptoms which impact 80% of women during the menopause transition and can last a mean of 7 to 10 years.[35] Improving vasomotor symptoms can consequently lead to improved sleep, physical activity, and overall quality of life, all factors that can affect response to weight loss interventions.[21] An additional consideration that can occur in observational studies is healthy-user

TABLE 2. *Mixed-model multiple regression analyses considering HT use, race, and depression and dyslipidemia diagnoses at baseline (model 1); and considering HT use, age, race, weight and diabetes diagnosis at baseline, and dietitian and behavioral psychology support (model 2)*

Model 1: Mixed-Model Multiple Regression Analyses Considering HT Use, Race, and Depression and Dyslipidemia Diagnoses at Baseline

	Model 1A: All Women (n = 106)				Model 1B: Women on High Dose of Semaglutide (n = 73)			
	β coefficient	95% CI		*P*	β coefficient	95% CI		*P*
HT use (yes vs no)	4.1	1.1	7	**0.007**	3.7	1.9	5.5	**<0.0001**
Race (White vs others)	0.4	−3	3.8	0.8	2	−0.3	4.1	0.05
Depression (yes vs no)	1.4	−0.8	3.5	0.2	0.5	1	2	0.5
Dyslipidemia (yes vs no)	−0.8	−2.9	1.3	0.5	−2.1	−3.5	−0.7	**0.004**
3 mo (vs 12 mo)	−8.3	−9.3	−7.4	**<0.0001**	−8.8	−10.8	−6.2	**<0.0001**
6 mo (vs 12 mo)	−3.7	−4.7	−2.8	**<0.0001**	−4	−5.9	−2	**<0.0001**
9 mo (vs 12 mo)	−1.9	−2.9	−0.9	**0.0002**	−2.3	−4.2	−0.3	**0.02**

Model 2: Mixed-Model Multiple Regression Analyses Considering HT Use, Age, Race, Weight and Diabetes Diagnosis at Baseline, and Dietitian and Behavioral Psychology Support

	Model 2A: All Women (n = 106)				Model 2B: Women on High Dose of Semaglutide (n = 73)			
	β coefficient	95% CI		*P*	β coefficient	95% CI		*P*
HT use (yes vs no)	3.4	1.8	5	**<0.0001**	4.1	2.4	5.7	**<0.0001**
Age (each 1-yr increase)	−0.01	−0.1	0.08	0.9	0.02	−0.08	0.1	0.7
Race (White vs others)	0.8	−1.2	2.7	0.4	2.3	0.3	4.3	**0.03**
Baseline weight (each 1 kg increase)	0.05	0.02	0.08	**0.003**	0.08	0.04	0.1	**<0.0001**
Diabetes (yes vs no)	−1.5	−3	−0.06	**0.04**	−1	−2.8	0.8	0.3
Dietitian visit (yes vs no)	−0.7	−2.1	0.8	0.4	0.6	−1.1	2.3	0.5
Psychology visit (yes vs no)	0.3	−1.8	2.4	0.8	−0.15	−2.5	2.2	0.9
3 mo (vs 12 mo)	−7.7	−9.3	−6.1	**<0.0001**	−8.7	−10.5	−6.9	**<0.0001**
6 mo (vs 12 mo)	−3.4	−5.1	−1.8	**<0.0001**	−4	−5.9	−2.2	**<0.0001**
9 mo (vs 12 mo)	−2.1	−3.8	−0.4	**0.01**	−2.2	−4.1	−0.3	**0.02**

Each model was performed in all women (n = 106, models 1A and 2A) and in women on high dose [a] of Semaglutide only (n = 73, models 1B and 2B).
HT, with hormone therapy; no-HT, without hormone therapy.
All *P* values <0.05 are considered significant.
The bold numbers signify significance, $P < 0.05$.
[a]High dose of semaglutide was defined as a dose of 1.7 to 2.4 mg weekly.

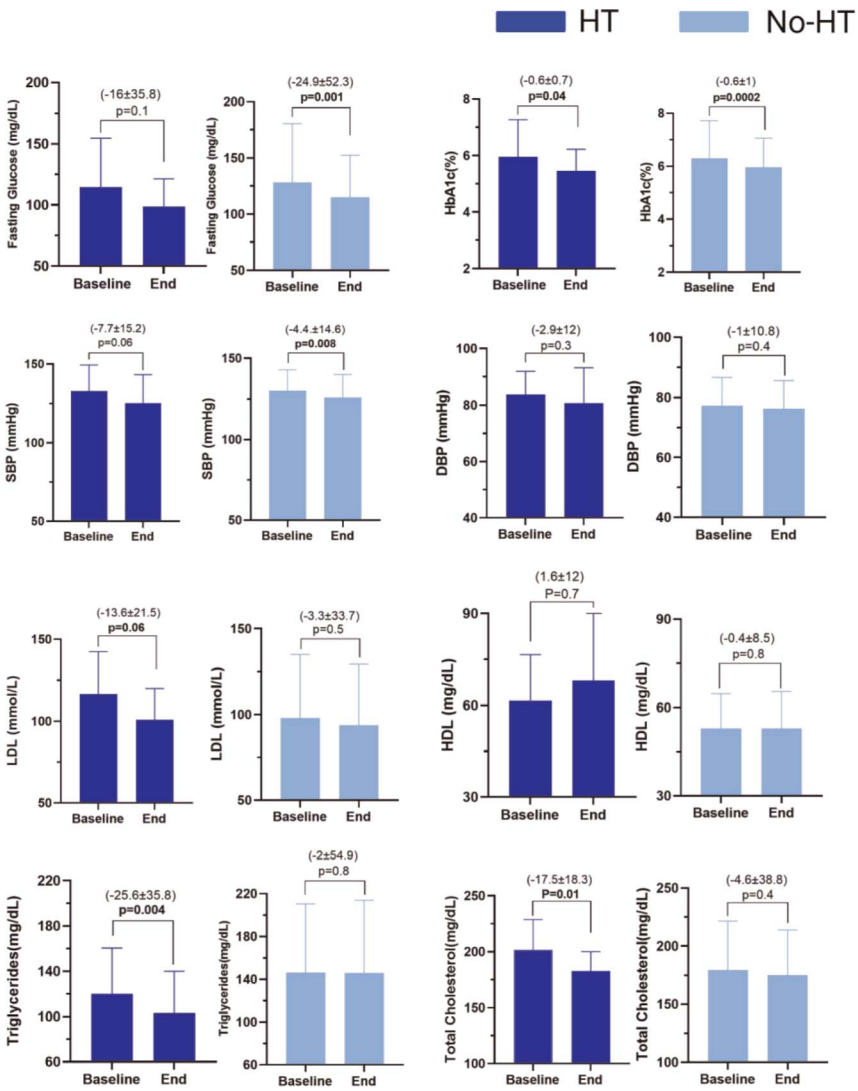


FIG. 3. Changes in fasting glucose, HbA1c, lipid profile, and blood pressure by hormone therapy use in all women (n = 106). DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HT, with hormone therapy; LDL, low-density lipoprotein; no-HT, without hormone therapy; SBP, systolic blood pressure; SD, standard deviation. All *P* values <0.05 are considered significant. Data in the figures are presented as mean ± standard deviation.

bias. Healthy-user bias arises when users of preventive medications are healthier due to factors other than medication effect.[36] This has been well established in research involving HT use, particularly as it relates to better CVD outcomes.[37-39] Compared to no-HT users, HT users generally pursue healthier lifestyle, are more physically active, leaner, and less likely to smoke, and have better access to medical care.[40,41] In this study, it is therefore possible that women on HT were more amenable to make healthier dietary changes and exercise more regularly.

In this study, we considered other potential confounders, including the use of weight-promoting medications. Weight-promoting medications can affect weight loss response to weight loss interventions. It is estimated that 11% of postmenopausal women take weight-promoting medications, and their use has been associated with greater increase in BMI and waist circumference during this stage of life.[42] In our study, the prevalence of weight-promoting medication use among HT users and nonusers was virtually the same, and thereby this variable may not explain the difference in weight loss outcomes among the two groups. Another important variable to consider, that this retrospective study was not able to fully assess, is the allostatic load. The allostatic load is a measure of cumulative biological risk as people age that can be associated with negative health outcomes and certainly blunted weight loss response to antiobesity interventions.[43] Our study did however compare certain components that are considered for the allostatic load calculation, including BMI, blood pressure, lipid profile, glucose, and HbA1c, with no differences among the two groups.

To date, there are no studies comparing weight loss outcomes to any of the antiobesity interventions, including semaglutide, among postmenopausal women with and without HT use. This study is relevant because menopause is associated with significant metabolic changes, including weight gain and body composition changes.[44] As the prevalence of overweight and obesity

among postmenopausal women increases, so does the risk of cardiometabolic diseases and CVD mortality.[45-47] Further, menopause, independent of aging, accelerates CVD risk.[24] Therefore, as CVD is the leading cause of death among women, there is a critical need to implement interventions to reduce this risk, including interventions that target excess adiposity. The importance of these interventions is further underscored by the fact that women spend one-half of their adult life in menopause, and as such, improving overall health and quality of life, and decreasing CVD risk is of utmost importance.[48]

The strengths of the study include a high level of detail regarding data collection. Although this study was limited by the observational and retrospective design, it is the first to assess the response to semaglutide among postmenopausal women with and without current HT use. Furthermore, we report data on cardiometabolic risk markers that may influence weight and overall health management in menopause. Our study has limitations. The retrospective nature of the study does not allow for the establishment of a causal relation between HT use and weight loss response to semaglutide or for the minimization of confounding factors. Despite including women across the Mayo Clinic Health system, our cohort included 106 women, and only a minority, 15%, were on HT. This is not surprising as the prescription rate of HT among women with clinical indications remains below 10%.[49,50] Although we observed significant differences in weight loss at all time points, our small sample size may have affected the statistical significance of some of our endpoints. Importantly, the sample size reflects the strict inclusion and exclusion criteria used to avoid potential confounders, which is a strength of this study. In addition, our study consisted of mostly White, college-educated women with no financial strain, potentially limiting the generalizability of the findings.

To establish a more definitive relationship between HT use and weight loss response to semaglutide in postmenopausal women, future prospective studies should incorporate the age at menopause; type of menopause; the duration, type, and dose of HT use; data on sleep quality, vasomotor symptoms, quality of life, activity, diet, and allostatic load; and the timing of semaglutide initiation in relation to HT initiation. Similarly, it would be interesting to investigate if there are differences in weight loss response to antiobesity medications among premenopausal, perimenopausal, and postmenopausal women not using HT (after adjusting for age and body composition), and if there are differences, if these are mitigated with HT use.

CONCLUSION

The menopause transition is associated with weight gain. As a woman's predicted lifespan continues to increase, women will spend a greater percentage of their lives in menopause. This, added to the fact that the obesity prevalence continues to rise in midlife women, underscores the importance of weight management interventions in postmenopausal women. In this study, HT use in postmenopausal women was associated with a greater weight loss with semaglutide. Larger studies are needed to confirm these results. Further, future studies are needed to identify the mechanisms behind this differential weight loss response. While the effect of HT use on body composition could partly explain this difference, additional mechanisms are probably involved, such as the effect of HT on sleep quality, vasomotor symptoms, and quality of life.

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