Baseline Levels of Estradiol (E2) and Estrone (E1) Differ by Age, Race, and BMI in the REPLENISH Trial

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Introduction

- Differences in endogenous E2 levels have been reported in menopausal women of different body mass index (BMI) and race[1-3]
  - Higher levels of E2 have been shown in overweight and obese menopausal women versus normal-weight postmenopausal women[1]
  - Higher E2 and E1 levels have also been reported in African-American versus White pre- and postmenopausal women[2,3]
- REPLENISH was a phase 3 trial (NCT01942668) that evaluated various doses of TX-001HR, an investigational, oral, 17β-estradiol/progesterone (E2/P4), softgel capsule (TherapeuticsMD, Boca Raton, FL), for treating moderate-to-severe vasomotor symptoms in menopausal women with a uterus

Objective

- To determine whether baseline levels of E2 and E1 in menopausal women differed by baseline age, race, or BMI among participants of the REPLENISH trial

Methods

- REPLENISH was a randomized, placebo-controlled, double-blind, multicenter trial that evaluated various doses of TX-001HR for the treatment of menopausal, moderate-to-severe vasomotor symptoms
- Healthy menopausal women aged 40 to 65 years with a BMI of ≤34 kg/m^2 were randomized to 1 of 4 E2/P doses (1 mg/100 mg, 0.5 mg/100 mg, 0.5 mg/50 mg, 0.25 mg/50 mg) or placebo
- E2 levels from serum taken at baseline were determined using liquid chromatography-tandem mass spectrometry, and were analyzed according to the following subgroups:
  - Age: <55 or ≥55 years
  - BMI: <25 kg/m^2, 25 to <30 kg/m^2, or ≥30 kg/m^2
  - Race: White, African-American, or other

Results

Participant Demographics and Subgroup Distribution

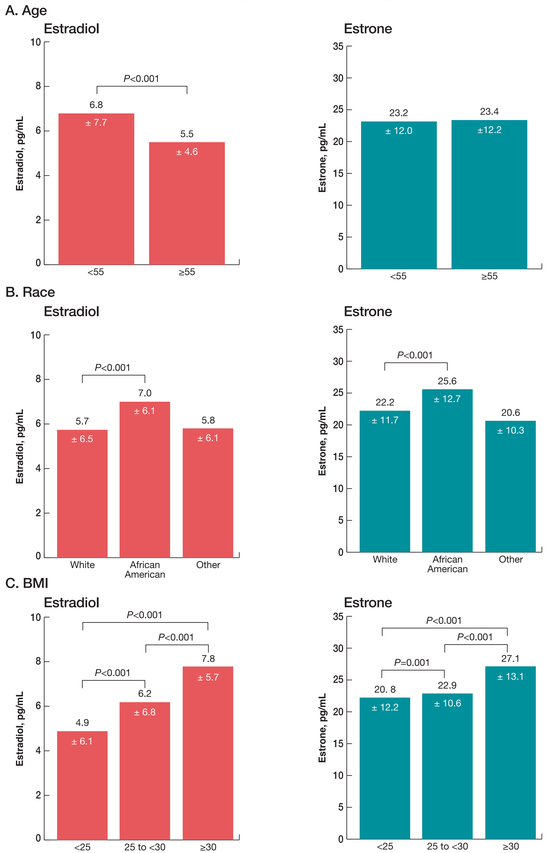
- All randomized women had a mean age of 55 years (range, 40-66 years) and a mean BMI of 27 kg/m^2 (range, 14.0–34.5 kg/m^2)
- Approximately half of the women were <55 and the majority were White (66%); the BMI group with the most women was 25 to <30 kg/m^2 (**Table 1**)

Table 1. Age, Race, and BMI Distribution of Study Participants

Parameter	n (%)
Age, y	
<55	924 (50.5)
≥55	906 (49.5)
Race	
White	1199 (65.5)
African American	587 (32.1)
Other*	44 (2.4)
BMI, kg/m^2	
<25	629 (34.4)
25 to <30	731 (40.0)
≥30	469 (25.6)

*Other includes other (n=20), Asian (n=12), American Indian or Alaska Native (n=6), Native Hawaiian or Pacific Islander (n=5), and unknown (n=2).

Figure 1. Mean E2 and E1 Levels in Age, Race, and BMI Subgroups



E2 and E1 Differences by Age, Race, and BMI

- Younger women (<55 years old) had significantly higher mean levels of E2 compared with older women (≥55 years old), while mean E1 levels did not significantly differ by age (**Figure 1**)
- African-American women had significantly higher mean levels of E2 and E1 than White women (**Figure 1**)
- Mean E2 and E1 levels were significantly different between the lowest versus the middle and highest BMI tertiles, and between the middle and highest BMI tertiles (**Figure 1**)
- Mean E2 and E1 values in each treatment group (TX-001HR doses and placebo) by age, race, and BMI subgroup are shown in Table 2 and Table 3, respectively
- No significant interactions for E2 and E1 levels were found between age and race (P=0.229 and P=0.306, respectively), age and BMI (P=0.246 and P=0.120), or race and BMI (P=0.391 and P=0.076)

Table 2. Mean Baseline Estradiol (pg/mL) Levels by Subgroup per Treatment Group

Subgroup		Estradiol / Progesterone				Placebo
		1 mg / 100 mg	0.5 mg / 100 mg	0.5 mg / 50 mg	0.25 mg / 50 mg	
Total n		415	424	421	424	151
Age						
<55	n	199	227	197	225	76
	Mean ± SD	6.72 ± 7.25	7.33 ± 8.84	6.58 ± 7.93	6.95 ± 7.59	5.37 ± 4.11
≥55	n	216	196	224	196	74
	Mean ± SD	5.88 ± 5.97	5.43 ± 4.55	5.03 ± 3.58	5.53 ± 4.09	5.90 ± 4.54
Race						
White	n	271	280	276	272	100
	Mean ± SD	5.84 ± 6.89	5.72 ± 6.56	5.44 ± 6.45	6.18 ± 6.86	5.24 ± 4.44
African American	n	134	136	133	139	45
	Mean ± SD	7.28 ± 6.18	7.79 ± 7.89	6.48 ± 5.35	6.60 ± 5.07	6.62 ± 3.98
Other	n	10	7	12	10	5
	Mean ± SD	5.02 ± 2.26	9.90 ± 14.03	5.07 ± 3.35	5.20 ± 2.51	4.57 ± 4.13
BMI, kg/m^2						
<25	n	144	149	135	147	54
	Mean ± SD	5.44 ± 7.08	4.54 ± 5.45	4.35 ± 4.98	5.43 ± 7.20	4.15 ± 3.63
25 to <30	n	154	158	184	170	65
	Mean ± SD	6.26 ± 7.34	6.46 ± 7.91	5.84 ± 6.77	6.23 ± 5.94	6.13 ± 4.79
≥30	n	117	116	102	103	31
	Mean ± SD	7.35 ± 4.66	8.90 ± 7.59	7.45 ± 5.60	7.54 ± 4.97	7.16 ± 3.67

Table 3. Mean Baseline Estrone (pg/mL) Levels by Subgroup per Treatment Group

Subgroup		Estradiol / Progesterone				Placebo
		1 mg / 100 mg	0.5 mg / 100 mg	0.5 mg / 50 mg	0.25 mg / 50 mg	
Total n		415	424	421	424	151
Age						
<55	n	199	227	197	225	76
	Mean ± SD	23.21 ± 13.25	23.09 ± 11.34	23.00 ± 13.61	23.56 ± 10.57	22.30 ± 10.39
≥55	n	216	195	224	196	74
	Mean ± SD	23.43 ± 11.98	23.57 ± 12.86	22.52 ± 12.38	23.65 ± 11.53	24.49 ± 11.84
Race						
White	n	271	279	276	272	100
	Mean ± SD	21.99 ± 12.87	21.43 ± 10.43	22.36 ± 13.34	22.95 ± 10.12	22.63 ± 10.54
African American	n	134	136	133	139	45
	Mean ± SD	26.25 ± 11.73	27.09 ± 14.04	23.92 ± 12.48	24.94 ± 12.58	25.84 ± 12.30
Other	n	10	7	12	10	5
	Mean ± SD	20.15 ± 9.99	25.24 ± 14.91	18.57 ± 7.54	22.68 ± 10.81	16.08 ± 8.41
BMI, kg/m^2						
<25	n	144	149	135	147	54
	Mean ± SD	20.78 ± 13.81	19.33 ± 8.86	21.39 ± 15.04	21.69 ± 10.88	20.94 ± 11.21
25 to <30	n	154	157	184	170	65
	Mean ± SD	22.82 ± 9.94	23.30 ± 12.05	21.90 ± 10.15	23.13 ± 10.32	24.07 ± 10.27
≥30	n	117	116	102	103	31
	Mean ± SD	27.12 ± 13.32	28.46 ± 13.66	26.08 ± 14.03	26.95 ± 11.58	26.19 ± 12.27

Conclusions

- Baseline levels of E2 were significantly higher in younger versus older women, in African-American versus White women, and in women with higher versus lower BMI. Mean E1 levels were similar to E2 levels, except for no significant difference between younger and older women
- The differences in E1 and E2 levels at baseline for race and BMI were independent
- These data are consistent with other studies showing higher levels of E2 in overweight and obese versus normal-weight postmenopausal women,[1] and higher E1 and E2 levels in African-American versus White women[2,3]
- Assessing differences in systemic hormone concentrations by demographics such as age, race, and BMI may elucidate potential differences in baseline health risks, and guide therapeutic dosing of menopausal hormone therapies for a more personalized approach to healthcare for women

Disclosures

- GC consults to pharmaceutical companies including but not limited to TherapeuticsMD and has stock options with TherapeuticsMD. SG, BB, and SM are employees of TherapeuticsMD (with stock/stock options). BB is also on the Board of TherapeuticsMD.
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