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Effects of hormones on skin wrinkles and rigidity vary by race/ethnicity: four-year follow-up from the ancillary skin study of the Kronos Early Estrogen Prevention Study

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Objective: To measure skin wrinkles and rigidity in menopausal women of varying race/ethnicity with or without hormone therapy (HT) for up to four years.
Design: Randomized, double-blind, placebo-controlled trial.
Setting: Academic medical centers.
Patient(s): Women (42–58 years of age) within 36 months of last menstrual period and enrolled in the Kronos Early Estrogen Prevention Study (KEEPS).
Intervention(s): Treatment with 0.45 mg oral conjugated equine estrogens (CEE), transdermal E_2 (50 μg/d) with micronized P (200 mg daily), or placebo for 4 years.
Main Outcome Measure(s): Skin wrinkles were assessed at 11 locations on the face and neck, and skin rigidity was assessed at the forehead and cheek at baseline and yearly for 4 years.
Result(s): Neither total wrinkle score nor total rigidity score was significantly different at baseline or over the 4-year follow-up among patients randomized to CEE, E_2, or placebo. Skin wrinkle and rigidity scores were primarily affected by race/ethnicity, with scores being significantly different between races for almost all of the wrinkle parameters and for all of the rigidity measures. There was no association between race and response to HT for total wrinkle or rigidity scores. Black women had the lowest wrinkle scores compared with white women across all 4 years. In general, skin rigidity decreased in all groups over time, but black women had significantly reduced total facial rigidity compared with white women after 4 years.
Conclusion(s): Race is the strongest predictor of the advancement of skin aging in the 4 years following menopause. HT does not appear to affect skin wrinkles or rigidity at most facial locations.
Clinical Trial Registration Number: NCT00154180. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Menopause, hormone therapy, skin wrinkles, skin rigidity, race

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Skin is the largest hormonally sensitive organ in the human body. Studies have shown that keratinocytes, Langerhans cells, melanocytes, sebaceous glands, and fibroblasts are under hormonal influence and that decreased estrogen levels, as occur in menopause, have been associated with decreased capillary blood flow in the skin (1). The aging of skin leads to decreased amounts of collagen, elastin, and hyaluronic acid (the three main components of the dermal tissue), with subsequent wrinkle formation and decreased skin rigidity. This loss of collagen has been shown to be accelerated in menopause, with an average decline of 2.1% in skin collagen per postmenopausal year (1).

Studies have shown increased collagen in women on hormone therapy (HT) and have suggested that E_2 may play a role in collagen synthesis and maintenance of hyaluronic acid (2, 3), but other studies have had conflicting results, making it difficult to draw conclusions (4). Nonetheless, dermatologists report that the positive effects of HT use are evident when examining skin during menopause (5). Our group has previously reported, in a pilot observational study of subjects who were ≥ 5 years into menopause, that long-term HT users have less severe wrinkling but decreased skin rigidity (6). These preliminary findings provided the impetus to test our hypothesis in a randomized controlled trial.

Additionally, it is widely accepted that there are racial and ethnic differences in the progression of skin aging (7–12), but studies have been limited. Several groups have argued that the higher melanin content in darker skin provides protection from damaging ultraviolet light and is the most likely explanation for the racial and ethnic differences observed in terms of skin aging (9–12). We previously reported that the Kronos Early Estrogen Prevention Study (KEEPS) ancillary skin patient population, an early postmenopausal population not yet on HT, demonstrated significant racial and ethnic differences in skin wrinkling at baseline exam, with black women having the lowest wrinkling scores (13).

The present study is the first prospective randomized trial to rigorously investigate the effect of HT use on skin wrinkling and rigidity. Our main objective was to determine if HT use in early postmenopausal women would affect wrinkle and rigidity scores compared with placebo. We also sought to determine if racial differences in early postmenopausal women would affect wrinkle and rigidity scores with HT use. We hypothesized that HT use in early postmenopausal women would decrease wrinkle scores and increase rigidity scores compared with placebo and that both skin parameters would vary significantly by race.

MATERIALS AND METHODS

KEEPS (NCT00154180) was a 5-year, multicenter, double-blind, randomized placebo-controlled trial designed to determine if early intervention with HT could prevent or delay heart disease in recently menopausal women (14). Subjects for the ancillary skin study were recruited from the parent KEEPS trial with Institutional Review Board approval at two of the nine original participating sites (Yale University and Albert Einstein College of Medicine; Supplemental Fig. 1, available online at www.fertstert.org). The objective of the ancillary skin study was to evaluate the effects of HT on skin wrinkles and skin rigidity in recently menopausal women. Written informed consent was obtained from each subject at enrollment. Race/ethnicity and baseline characteristics (sun exposure, use of tanning beds, use of sunscreen, current smoking or history of smoking, vitamin use, moisturizer use, and other skin products/prescriptions) were self-reported. In addition to the inclusion/exclusion criteria previously reported for the parent trial (14), the ancillary skin study excluded women who reported a history of scleroderma, collagen disorders, facial trauma, facial plastic surgery, and use of Botox injections, chemical peels, or dermabrasion therapy. Women were also excluded if they reported taking androgens, long-term topical or systemic steroids, or retinoids. Women who met the inclusion and exclusion criteria were randomized to either placebo, 0.45 mg oral conjugated equine estrogens (CEE), or 50 μg transdermal E_2. All women in the parent KEEPS trial had intact uteri, because hysterectomy was an exclusion criterion. All participants were administered combined HT with continuous estrogen formulation and cyclic 200 mg micronized P or placebo (14). Patients and providers were blinded to treatment allocation.

Our main outcome measures were facial wrinkle and skin rigidity scores. These skin parameters were measured at baseline before randomization and yearly for 4 years of follow-up. Wrinkle scores were assessed with the use of the Lemperle scale, which is an objective visual scoring system where skin wrinkles are assessed at 11 distinct locations on the face (horizontal forehead, glabellar frown, cheek folds, preauricular lines, periorbital lines, nasolabial folds, upper lip lines, corner of mouth lines, marionette lines) and neck (chin crease and neck fold) (15). Wrinkle severity at each location was graded on a scale of 0 (none) to 5 (severe), and the sum of the individual scores provided the total wrinkle score. A durometer (Acor Orthopaedic) was used according to the manufacturer's protocol to assess skin rigidity at the midpoint of the forehead and at the midpoint of the cheek (2 cm inferior to the orbital ridge in the midpupillary line). The sum of these two rigidity scores provided the total rigidity score.

Baseline characteristics were compared between treatment groups and by race with the use of paired t tests and Fisher exact test. Changes in skin parameters from baseline to 4 years were analyzed with the use of paired t tests, with comparisons between treatment groups assessed with the use of repeated-measures analysis of variance. Generalized linear models were used to evaluate the effects of treatment, race, changes over time, and potential interactions among treatments, race, and time. These models used all measurements taken over time (baseline and 12, 24, 36, and 48 months) and took into account correlations both within subjects and between subjects. All statistical analyses were done following the principles of intention to treat. SAS version 9.4 (SAS Institute) was used for all statistical analyses.

RESULTS

Demographics

There were 116 early menopausal women enrolled in the KEEPS ancillary skin study. The population mean age was