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ORIGINAL STUDY

Benefits for cardiovascular system, bone density, and quality of life of a long-term hormone therapy in hysterectomized women: a 20-year follow-up study

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Abstract

Objective: The safety, consequences, and dosage of long-term hormone therapy (HT) for postmenopausal women remain unclear. Our aim was to analyze the effects of HT after 20 years of therapy in women after hysterectomy, focusing on the symptoms of menopause, blood pressure, lipid profiles, and bone density.

Methods: A prospective observational longitudinal study was designed. The initial transdermal estradiol dose was reduced in half (0.025 mg/d) at 60 years of age. Different parameters including demographic, cardiovascular, bone density, and metabolic variables, as well as quality of life characteristics, were analyzed using bivariate analyses. Multivariate generalized estimating equations for longitudinal data were fitted for differences over time and between doses (<60 vs ≥60 y) using the R package geepack.

Results: After 20 years of HT, the mean age of 56 studied hysterectomized women was 67.1 years. The mean Kupperman index score decreased from 26.7 to 12.0 ($P < 0.001$). A trend with total and low-density lipoprotein cholesterol reduction and high-density lipoprotein cholesterol increase was observed over time. A decrease in very-low-density lipoprotein cholesterol ($P = 0.05$) and an increase in T score vertebral densitometry ($P = 0.014$) were detected after HT. No changes in health outcome were detected in women older than 60 years with the reduced dose of HT. Breast cancer was the reason for dropouts in 0.02% women.

Conclusions: HT for up to 20 years after hysterectomy may be beneficial for bone and cardiovascular health and for the overall quality of life. Our data suggest the importance of evaluating the dose and the timing of HT.

Key Words: Cardiovascular – Hormone therapy – Hysterectomy – Long-term effects – Postmenopause.

Menopause is a natural part of biological aging in women that occurs, in most cases, between the ages of 46 and 55 years.[1] In menopause, the physiological decline in estrogen levels is associated with vasomotor symptoms or hot flashes, and sleep disruption, which may even persist for a decade or longer after menopause onset.[2] The symptoms also include sexual dysfunction, decreased libido, loss of skin elasticity, mood disorders, bone density loss, and increased cardiovascular risks.[3] This wide range of symptoms and changes considerably affects the overall quality of life of a large number of women worldwide. In addition, postmenopausal women are unique because their health risks increase not only because of aging but also owing to the loss of estrogens. Therefore, the health care system should be capable of guiding women and providing help that will improve their personal

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and public life.[4] In particular, the use of hormone therapy (HT) is considered a potential therapeutic and protective strategy.

Since its approval by the Food and Drug Administration in 1942, there has been an ongoing debate about the benefits and negative side effects of HT. There is wide consensus that HT is the most effective therapy for vasomotor symptoms and genitourinary syndrome of menopause, as well as for preventing bone loss and fractures.[5] Despite many years of clinical application of HT, many women discontinued HT after the Women's Health Initiative (WHI) in 2002 reported an overall increased risk of breast cancer.[6] However, several follow-up studies and reevaluation of the WHI results raises considerable doubt on the validity of its conclusions. In fact, there is an agreement that the benefits of HT exceed the associated risks in women who initiate treatment before the age of 60 years and/or at least within 10 years after the onset of menopause.[7] Undoubtedly, HT reduces the mortality and the incidence of cardiovascular diseases in this group of postmenopausal women.[5,8] However, the debate about increased breast cancer risk with HT is still ongoing. A recent systematic review indicated a positive association between HT and breast cancer.[9] In turn, the use of estrogen was associated with lower incidence.[10] However, fewer than half of women in surgical menopause receive estrogens.[11]

Although life expectancy in women has increased by more than 6 years in the last 20 years, the effect of long-term HT and the decrease in dose after 60 years of age have not been assessed yet. In fact, there are few studies analyzing the effect of HT after 20 years of treatment or exploring the changes after the dose reduction at 60 years of age. Therefore, it is necessary to explore the impact of HT beyond the age of 60 years and its long-term administration.

The aim of this prospective 20-year follow-up study was to investigate the effect of long-term HT on menopause symptoms, blood pressure, lipid profiles, and bone density in hysterectomized women even after halving the dose at 60 years of age.

METHODS

Study design and setting

This is a prospective observational 20-year follow-up study done according to the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology.[12] In this study, postmenopausal Spanish women who attended the only menopause medical unit in Granada (Spain) at Hospital Universitario San Cecilio were recruited from September 1989 to May 1998 and were monitored for 20 years. This project was approved by San Cecilio University Hospital Ethical Committee of Granada and was conducted in accordance with the Declaration of Helsinki. When the benefit-risk ratio was favorable, women received HT with 0.050 mg/d of transdermal estradiol, and HT was maintained for 20 years in all women in the study. However, when women turned 60 years old, the initial estrogen dose was reduced to 0.025 mg/d, the lowest effective dose recommended. After the first medical visit (t0), women were followed annually for 20 years in the menopause medical unit. Only women who completed the 20-year follow-up, including changes in doses from 60 years of age, were included in the study. All the assessments were performed by the same physician using the same standard diagnostic tests for all the participants.

Data sources and variables

Sociodemographic (sex and age) and clinical data were verified from clinical records and measured during each consultation through blood tests, bone density assessment, mammograms, and sonography. Clinical data included cardiovascular parameters such as body mass index (BMI), total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very-low-density lipoprotein cholesterol (VLDL), triglycerides, and systolic and diastolic blood pressure. T score of vertebral densitometry and incidence of fractures were determined for bone outcomes. Breast cancer assessment was achieved through mammography and/or sonography. In addition, information on time since menopause onset, type of menopause, quality of life according to menopause symptom intensity (Kupperman index), baseline hormonal and metabolic parameters, breast cancer risk factors, and lifestyle were collected with self-reported questionnaires. All these parameters were collected each 5 years since recruitment at the first visit. Therefore, the first visit corresponded to the t0 (time point "0") of the follow-up, the visit at 5 years after first visit corresponded to t1, at 10 years to t2, at 15 years to t3, and, finally, at 20 years to t4.

Kupperman index was used to measure the severity of 11 menopausal symptoms. On this scale, menopause symptoms included hot flashes, night sweats, sleep difficulty, irritability, depression, dizziness, lack of concentration, joint pain, headache, palpitations, and vaginal dryness. Each symptom was rated according to its severity as follows: no symptom, 0 to 14; weak, 15 to 20; moderate, 21 to 35; and severe, 36 to 51. The total Kupperman index score was the sum of the individual symptom scores. A total score of 15 or higher was considered as indicative of menopausal syndrome.[13]

BMI was calculated from self-reported data on current weight and height (kg/m^2). The following categories of BMI were defined according to the standard World Health Organization (WHO) classification: normal, 18.5 to 24.9; overweight, 25 to 29.9; obesity I, 30 to 34.9; obesity II, 35.0 to 39.9; and obesity III, ≥40 kg/m^2.[14]

The levels of total cholesterol, LDL, VLDL, and triglycerides below 200 mg/dL, 100 mg/dL, 30 mg/dL, and 150 mg/dL, respectively, were considered desirable. As for HDL, the desirable level was considered to be greater than 50 mg/dL.[15]

Blood pressure lower than 120/80 mm Hg was considered as healthy. In contrast, according to WHO guidelines, blood pressure was considered to be high if the systolic measurement was 140 mm Hg or higher and/or the diastolic measurement was equal or higher than 90 mm Hg.

Bone mineral density was measured by means of dual x-ray absorptiometry. As defined by the WHO, osteoporosis is present when bone mineral density is 2.5 SD or more below the average value for young healthy women (a T score of <−2.5 SD). In addition, fractures in spine, hip, wrist, or shoulder, the relevant clinical sequelae of osteoporosis, were noted.

To calculate the breast cancer risk, we used data from the Andalucia-Granada Cancer Registry. The probability for women in Granada to have breast cancer is 1 in 83 before 45 years of age, 1 in 48 before 50 years, 1 in 31 before 55 years, 1 in 24 before 60 years, and 1 in 18 before 65 years.

Data analysis

First, descriptive analyses were conducted to characterize the samples. Absolute (n) and relative (%) frequencies were calculated for qualitative variables, and means (x) and SD, or medians and interquartile ranges were calculated for quantitative variables when necessary.

Second, bivariate analyses were performed. Although age is the key risk factor associated with the worsening of the studied clinical variables, we used time point t0 before the treatment as a control for the variables measured at different time points during the treatment of the same patient to avoid genetic or socioeconomic differences. Thus, the bivariate analysis was focused on comparing the subject in the cohort at the time of the first visit (t0) with the same subject at time of the end of the follow-up (t4). For that purpose, McNemar tests were performed to compare qualitative variables, and paired sample T-tests were performed to compare quantitative variables.

In addition, we performed multivariate generalized estimating equations (GEE) models, as an approach for fitting marginal generalized linear models to clustered data (in our study, clusters are individuals because observations are different visits from the same individuals). These models are especially recommended for longitudinal data when the study sample is not very large, but there are several repeated measures (in our case, five visits).[16] The GEE approach focuses on models for the mean of the correlated observations within clusters without fully specifying the joint distribution of the observations.[16] For this study, the main outcome used as dependent variables for analyses was time (from visit 0, without HT, to visit 4, after 20 years of receiving HT). This analysis allows us to find differences and tendencies during the different follow-up times (at 5, 10, 15, and 20 y of treatment). Finally, all models were adjusted for age at change of doses (<60 vs ≥60 y) and were graphically divided into these two subgroups. All analyses were performed using R software.[17] For GEE models, the R package geepack was used.[16]

RESULTS

Demographic and follow-up data

A total number of 259 hysterectomized women were treated with HT (Fig. 1). During prospective follow-up, 203 postmenopausal women discontinued HT because of misinformation as the main reason (95 of 203 [46.8%]). Stroke, which has a high association with HT, developed only in one woman after follow-up t2. In addition, heart disease and hypertension were the cause of four more dropouts. The highest number of HT dropouts (54 of 203 [26.6%]) occurred after t1 but decreased over time. In fact, only 21 women discontinued HT at time point t3. Almost half of them indicated that they dropped out because of their age, with the mean age being 65.1 years.

At the time of data analysis, HT had been administered for 20 years without missed treatments reported and evaluated annually in 56 postmenopausal women with hysterectomy. In particular, 51 women initiated HT after a hysterectomy with adnexectomy, so these women were in menopause after surgery. Only five women had a history of simple hysterectomy, naturally reaching menopause later. The most common indications for hysterectomy included the following: 86% (48 of 56) benign process and 14% (8 of 56) gynecological cancers, (3) cervix, (3) ovarian, and (2) uterine sarcoma. HT was initiated in women with mean ± SD age of 46.8 ± 6.6 years and was maintained for 20 years until 67.2 ± 6.7. At the date of analysis, 49 women older than 60 years were receiving HT. The mean time from menopause onset to initiate HT in 51 women (91.1%) was 2 years, well within the standard recommendation of 10 years.

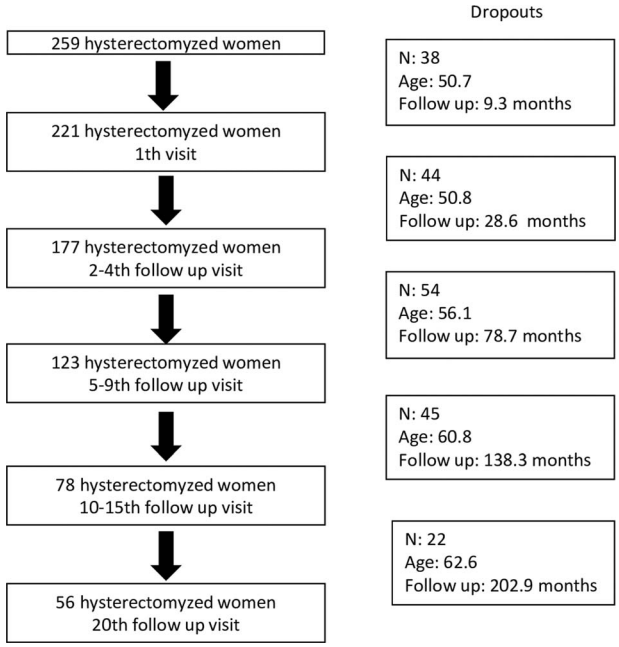

FIG. 1. Flow chart of selection process of hysterectomized women with HT for 20 years and dropouts. After the first medical visit, women were followed annually for 20 years in the menopause medical unit. HT, hormone therapy.

Long-term benefits of HT despite dose reduction after the age of 60 years

All the parameters analyzed in this study at baseline (t0) and follow-up visit after 20 years of HT (t4) are shown in Table 1. Climacteric symptoms, measured by Kupperman index, were significantly lower ($P < 0.001$) in women after HT when compared with 20 years earlier. Before HT, the mean ± SD value of Kupperman index was 26.8 ± 11.4, and 66.7% of women exhibited moderate/severe symptoms (score, >20). These values rapidly decreased since follow-up visit t1 and continued to decrease even after estrogen dose halving (Fig. 2A). After HT, only eight women (14.9%) presented with moderate/severe symptoms. We observed changes in the average BMI of women after HT from 29.1 kg/m^2 to 30.9 kg/m^2 ($P < 0.001$). In addition, our results showed that LDL levels significantly decreased ($P < 0.008$) after 20 years of HT, even in women older than 60 years with the estrogen dosage reduced in half (Fig. 2B). Despite the aging, total cholesterol and VLDL levels decreased ($P = 0.099$ and $P = 0.068$, respectively) after HT (Fig. 2C, D). Transdermal estradiol did not affect triglyceride levels as expected. Although HT use was not found to be statistically associated ($P = 0.199$) with HDL, these levels increased over time (Fig. 2E). Therefore, HT in postmenopausal

TABLE 1. *Baseline (t0) and follow-up visit after 20 years of HT (t4) characteristics of postmenopausal women included in this study*

Parameter	t0	t4	*P*
Weight, mean (SD)	71.9 (11.4)	73.6 (11.0)	0.043[a]
BMI (kg/m^2), mean (SD)	29.1 (4.99)	30.9 (5.33)	<0.001[a]
DV: normal, n (%)	13 (26.3)	8 (14.5)	<0.001[b]
Overweight, n (%)	18 (32.7)	21 (38.2)	
Obesity I, n (%)	17 (30.9)	13 (23.6)	
Obesity II-III, n (%)	7 (12.7)	13 (23.7)	
Kupperman index, mean (SD)	26.7 (11.4)	12.0 (7.9)	<0.001[a]
DV: no symptoms (0-14), n (%)	10 (18.5)	39 (72.2)	<0.001[b]
Weak (15-20), n (%)	8 (14.8)	7 (13.0)	
Moderate (21-35), n (%)	19 (35.2)	7 (13.0)	
Severe (36-51), n (%)	17 (31.5)	1 (1.9)	
Kupperman index, dicot.			
DV: no symptoms, n (%)	10 (18.5)	39 (72.2)	<0.001[b]
Symptoms, n (%)	44 (81.5)	15 (27.8)	
Cholesterol, mean (SD)	220.4 (37.0)	211.1 (33.7)	0.099[a]
DV (<200 mg/dL), n (%)	18 (32.1)	19 (33.9)	1.000[b]
≥200 mg/dL, n (%)	38 (67.9)	37 (66.7)	
Triglycerides, mean (SD)	108.5 (52.6)	115.7 (50.8)	0.301[a]
DV (<150 mg/dL), n (%)	46 (82.1)	43 (76.8)	0.549[b]
≥150 mg/dL, n (%)	10 (17.9)	13 (23.2)	
LDL, mean (SD)	137.1 (32.7)	123.6 (24.9)	0.008[a]
DV (<100 mg/dL), n (%)	5 (8.9)	9 (16.1)	0.212[b]
≥100 mg/dL, n (%)	51 (91.1)	47 (83.9)	
VLDL, mean (SD)	24.0 (11.6)	20.2 (4.9)	0.068[a]
DV (<30 mg/dL), n (%)	28 (82.4)	33 (97.1)	0.125[b]
>30 mg/dL, n (%)	6 (17.6)	1 (2.9)	
HDL, mean (SD)	60.3 (14.7)	66.4 (14.00)	0.199[a]
DV >50 mg/dL, n (%)	48 (85.7)	50 (89.3)	0.754[b]
<50 mg/dL, n (%)	8 (14.3)	6 (10.7)	
Blood pressure (systolic) (mm Hg), mean (SD)	136.8 (20.0)	141.3 (20.3)	0.126[b]
Blood pressure (diastolic) (mm Hg), mean (SD)	83.4 (10.5)	77.1 (9.0)	<0.001[b]

BMI, body mass index; DV, desirable values; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; VLDL, very-low-density lipoprotein cholesterol.
[a]Paired *t* test (Student's *t* test).
[b]McNemar test.

women, even at low doses, led to profound and beneficial changes in plasma lipids. Furthermore, postmenopausal women treated with estrogens had lower diastolic blood pressure than 20 years earlier ($P = 0.001$). Altogether, these results suggest that long-term HT, even with lower dosage, decreases the risk of cardiovascular disease.

In regard to bone examinations, bone mineral density data were not available until the follow-up time point t3. However, we observed a significant bone mineral density increase in the last follow-up visit, maintained even when the dosage was lowered (Fig. 2F). Interestingly, the cohort did not possess a low BMI, which is a well-established risk factor for fracture in postmenopausal women.[18] In agreement with that, none of these women had fractures.

During prospective follow-up, only 0.02% of women discontinued HT because of breast cancer diagnosis. These four postmenopausal women developed breast cancer with a mean age of 62 years. In particular, during the 10 first years of HT, two breast cancer cases were detected in women whose mean age was 59.5 years. After 14 and 18 years of follow-up, two more cases were diagnosed with a mean age of 64 years. According to the mean age of our cohort after HT during 20 years and the incidence of breast cancer in Granada, we would expect 3.1 cases of breast cancer. Interestingly, only one woman had breast cancer at 60 years of age after long-term HT during 20 years. Based on these results, we conclude that the use of long-term HT was not associated with breast cancer in our cohort.

DISCUSSION

HT is the most effective treatment option available for women experiencing classic menopausal symptoms, but HT prescription is based on personalized decision making. There are several factors to consider including age, severity of symptoms, improving quality of life, and the participant's calculated risk for cardiovascular disease, osteoporosis, and breast cancer.[19] In this study, HT was continued for 20 years in hysterectomized women, decreasing the dose from 0.050 to 0.025 mg/d transdermal estradiol at 60 years of age. Importantly, it exceeded the standard recommendation about HT duration for 5 years.[20] However, here, we confirm a decrease in cardiovascular risk and bone fractures in women treated with HT. Interestingly, several benefits including lipid profile, blood pressure, and bone density persisted even with halving the dosage at 60 years of age. Therefore, the benefits of HT for more than 20 years widely outweighed its attributable risks in our cohort.

Despite the fact that women's longevity is increasing worldwide, there is an information gap in menopausal guidelines when considering long-term HT for women older than 60 years. In addition, the general recommendation of HT for less than 5 years remains insufficient for women with early menopause. In fact, women who become menopausal before 45 years of

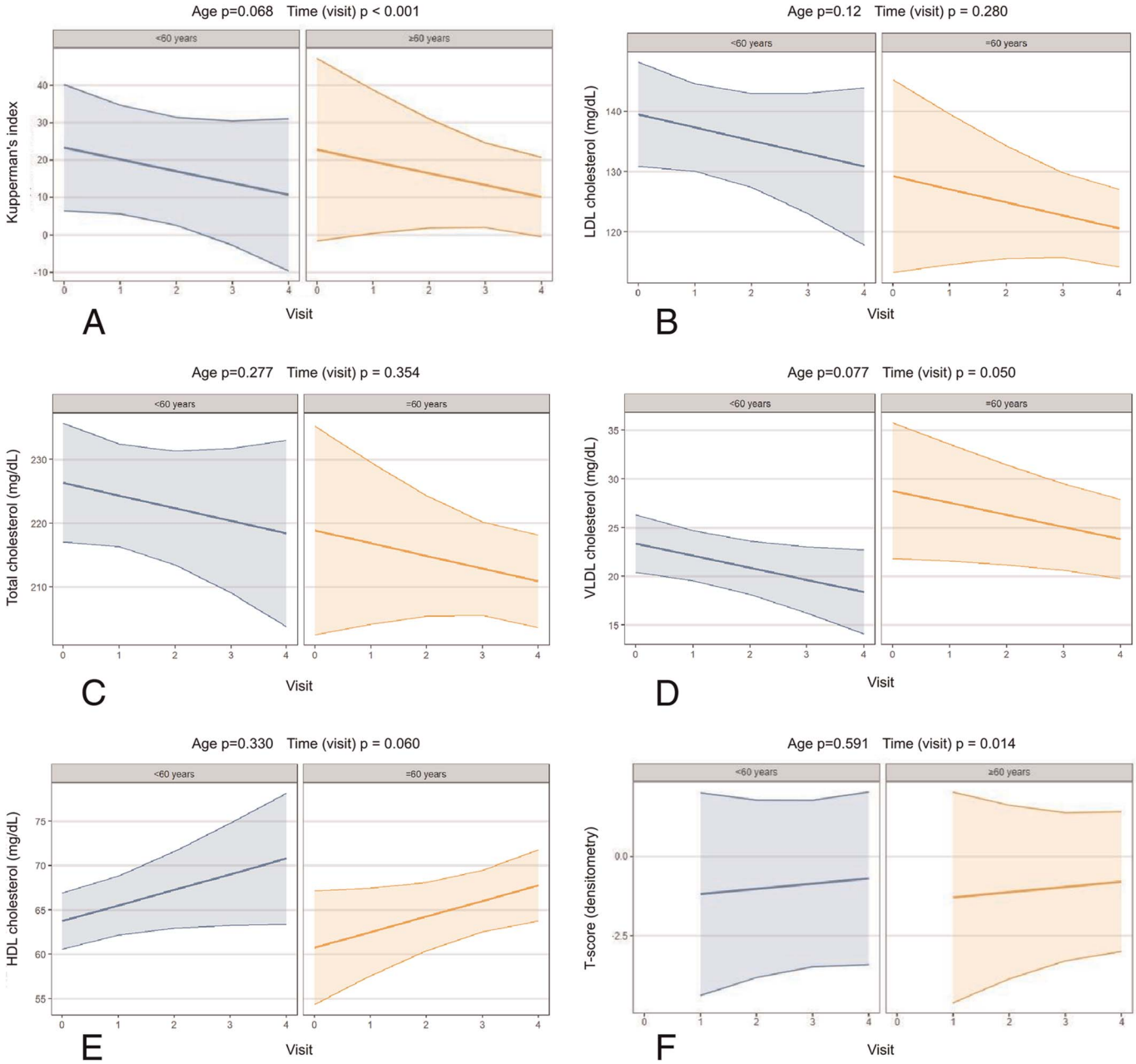

FIG. 2. Graphical analysis of multivariate GEE models of each outcome variable ((**A**) Kupperman index; (**B**) LDL cholesterol; (**C**) total cholesterol; (**D**) VLDL cholesterol; (**E**) HDL cholesterol; and (**F**) T score) adjusted for time (visit) and age. The tendencies are shown separately for women younger than 60 years and older than 60 years, respectively, according to differences in therapy doses. Visits 0, 1, 2, 3, and 4 correspond to initial visit, visit at 5 years, 10 years, 15 years, and 20 years respectively. GEE, generalized estimating equations; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; VLDL, very-low-density lipoprotein cholesterol.

age as a consequence of surgical or medical procedures display a more complex physiological situation, but surprisingly, they are less likely to start HT or continue it long-term.[21] In accordance with Wilson,[22] the main objective of HT is to slow down the rate of aging, which starts earlier in these women, and to ensure the compromised general systemic health of postmenopausal women. With the present study, we reveal that HT might provide enormous benefits to women's health without increasing the risk of breast cancer. Therefore, our results suggest the importance of starting HT as soon as possible and maintaining it throughout women's lifetime. In agreement with our study, other work suggests that there is no need to impose an age limit as long as an effective minimum dose is used.[23] Our findings provide new data indicating clinical benefits of prolonged HT in postmenopausal women older than 60 years as a primary preventive therapy for cardiovascular and bone diseases. It suggests a therapeutic strategy for clinicians and gives new possibilities to improve quality of life of women in spite of aging.

Based on our results, HT may be suitable for women in menopause from different points of view. First, there is a 10-year

delay in the peak of coronary heart disease in women as compared with men, whereas the highest incidence of myocardial infarction and sudden death in women is noted 20 years later than in men.[24] This delay in onset seems to be due to the cardioprotective effects of endogenous estrogen in women. Hence, HT would aid in preventing cardiovascular disease in menopausal women, as we demonstrate in this work. Second, use of conjugated equine estrogen in women with previous hysterectomy has been significantly associated with reduced breast cancer incidence and mortality.[10] In this sense, we showed in our cohort that the frequency of breast cancer in women with HT was not higher than the population frequency, although analytic longitudinal studies with no-treatment control group are required to corroborate this descriptive observation. Finally, postmenopausal osteoporosis is caused by the deficiency of estrogen, making women more susceptible to osteoporosis than men.[25] After long-term HT, we observed a beneficial increase in bone density. Interestingly, HT has been recently associated with improved delayed memory, mitigating the higher life-time risk of Alzheimer disease.[26] Altogether, these results are contrary to the main findings of the WHI study. The administration of conjugated equine estrogen in WHI cohort versus transdermal estradiol in our study may have an impact on these differences. In fact, in the WHI study, progestin was administered to women who did not have a hysterectomy. In addition, the WHI study presented several limitations that have been previously disclosed.[27] For instance, few postmenopausal women completed long-term HT. Moreover, women enrolled in the WHI study were on average 12 years postmenopause, with a mean age of 63 years. Therefore, significant vascular disease may have already been present at the time of therapy initiation, and HT may not reverse established pathological changes. In fact, subsequent analysis demonstrated that this risk was influenced by the woman's age and time since menopause. Furthermore, WHI results did not evaluate the mortality or the causal link between HT and breast cancer. Such inconsistencies in WHI guidelines may explain the regained acceptance of HT, with a steady increase in the number of women receiving their first prescription for HT.[28]

The present study also possesses several limitations to consider in future research. We did not compare with a control group without HT, which is a reason for further study. Nevertheless, we approached this issue by comparing each woman at different time points to reduce the variability between the study subjects. In addition, our sample size was not optimal, and all participants were selected from the same hospital. It is important to note that, since we conducted a prospective 20-year follow-up study, it was very difficult to reach a large portion of the cohort. Therefore, we decided to avoid a retrospective large size study to gather homogeneously and comprehensively all the variables of interest. To resolve this issue, we performed a specific multivariate analysis recommended for low sample-size studies with many temporal measures (GEE models). No censoring data were present because we only included women who completed the 20-year follow-up. That could introduce a selection bias, and therefore, our results might be only applicable to women with better health conditions that continued the treatment. Finally, we cannot discount the presence of residual confounding, as relevant covariates like cotreatments were not included in the models. Considering that our study was conducted in a sample from Granada, extrapolation of the results to other populations might be compromised. Additional longitudinal studies in different populations might be necessary to corroborate our results. We included the variables that a priori could be confounders of our association. Nevertheless, nonmeasured variables could bias the results, as it occurs in any observational study.

CONCLUSIONS

Our data suggest the beneficial effects of long-term HT using transdermal estradiol when initiated close to the beginning of the menopause and maintained after 60 years of age in women after hysterectomy. These benefits would include improvements in menopause symptoms, lipid profile, blood pressure, and bone density and may be maintained with a reduced-dose therapy after 60 years of age.

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