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Hormone Therapy and Urine Protein Excretion: A Multi-racial Cohort Study, Systematic Review and Meta-Analysis

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Abstract

Objective—Experimental models suggest estrogen has a renoprotective effect, but human studies show variable results. Our objective was to study the association of hormone therapy (HT) and albuminuria in post-menopausal women and to synthesize the results with outcomes from prior studies.

Methods—We analyzed data from post-menopausal women who participated in the second study visit (2000-2004) of the Genetic Epidemiology Network of Arteriopathy (GENOA) study. The exposure was self-reported HT use and the outcome was albuminuria (urine albumin-to-creatinine ratio > 25 mg/g Cr). We also conducted a systematic review and meta-analysis on the association of HT and urine protein in post-menopausal women. Continuous and dichotomous measures of protein excretion were converted to a standardized mean difference (SMD) for each study.

Results—In the GENOA cohort (n = 2217), there were fewer women with albuminuria amongst HT users than non-users (9% vs. 19%, p<0.001). HT use was associated with decreased odds of albuminuria (OR 0.65, 95% CI 0.45-0.95), after adjusting for significant differences in age, race, education, co-morbidities, and the age at and cause of menopause. The SMD of the effect of HT on urine proteinuria/albuminuria in the RCTs (n=3) was 0.02 (95% CI -0.29-0.33) and -0.13(95% CI -0.31-0.05) in the observational studies (n=9). There was significantly less albuminuria among HT users (SMD -0.15, 95% CI -0.27- -0.04) in the 9 studies that only reported albuminuria as an outcome and in the 10 studies with a comparator arm (SMD -0.15 (95% CI -0.26- -0.04)).

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Conclusions—HT is associated with decreased odds of albuminuria, but some of the observed benefit may be related to reported outcomes, the presence of a comparator arm and the type of study design.

Keywords

estrogen; hormone therapy; albuminuria; proteinuria; albuminuria

Introduction

Several observational studies have demonstrated a slower decline of kidney function in women with renal disease as compared to men, particularly before the age of menopause.(1-5) Animal studies have shown that sex hormones play an important role in kidney function. In general, estradiol seems to have anti-fibrotic, anti-inflammatory and vasodilatory properties in the kidney.(6, 7) Taken together, this body of evidence has implicated estrogen as a potential renoprotective agent.(8)

Elucidating the role of estrogen in human kidneys is challenging given the complex, multisystemic effects of estrogen and other physiologic changes around menopause. Studies evaluating the association of estrogen-containing hormone therapy (HT) and kidney function, in particular proteinuria and albuminuria, have shown mixed results. Some studies have shown that women using HT have an increased risk of having albuminuria (9, 10), while others have demonstrated a substantially decreased risk.(11, 12) The conflicting results in this area may be due to differing study designs, inclusion and exclusion criteria, and definitions of exposure and outcomes.

In the current study, we used a large, racially and ethnically diverse cohort to study the association of HT and albuminuria. We chose albuminuria as our main outcome of interest as it is an early marker of renal dysfunction and is also associated with cardiovascular disease risk.(13-15) Our objective was to evaluate whether HT use was associated with a decreased risk of albuminuria, after controlling for known risk factors for chronic kidney disease. We also conducted a systematic review and meta-analysis to identify all available studies on HT and proteinuria or albuminuria to see if we could explain the heterogeneity in the existing literature.

Materials and Methods: GENOA

Study Design and Participants

This study included post-menopausal women who participated in the Phase II study visit of the Genetic Epidemiology Network of Arteriopathy (GENOA) study from 12/2000 to 11/2004.(16) GENOA is one of 4 networks in the Family Blood Pressure Program, a multi-center study investigating the genetics of hypertension.(16) GENOA recruited participants of different races and ethnicities from 3 sites: African-Americans from Jackson, MS, Mexican-Americans from Starr County, TX and non-Hispanic whites from Rochester, MN. Sibships with at least 2 hypertensive individuals diagnosed before age 60 were recruited. As part of an effort to reduce confounding during recruitment, the GENOA sibships recruited from

Starr County, TX had to have at least 2 siblings with diabetes, given the high incidence of diabetes in this population. All full biologic siblings of recruited siblings were invited to participate in the study. This cross-sectional, post-hoc analysis included post-menopausal participants from GENOA (n=2036 out of 4329 total participants, excluding men and pre-menopausal women). We did not have complete data on albuminuria in the other networks and so they were not included.

Study Visit

All participants gave informed consent and the Institutional Review Board at each clinic site approved all protocols. Questionnaires were administered via personal interviews with trained examiners. They underwent a standard physical exam, blood and urine tests. Body Mass Index (BMI) was calculated as weight (kg)/height $(m)^2$. The diagnosis of hypertension was confirmed if the average of 3 systolic blood pressures (BP) or diastolic BPs were greater than 140 or 90 mm Hg respectively, or if there was a prior diagnosis of hypertension and use of prescription anti-hypertensive medication was documented, including the use of renin-angiotensin-aldosterone (RAAS) blockers. The diagnosis of diabetes was determined by self-report and an ‘ever smoked’ status was defined as having smoked >100 cigarettes at any point in the participant's lifetime. The highest grade of completed education was recorded.

Laboratory Methods

Blood was drawn by venipuncture and urine was collected after an overnight fast of at least 8 hours. Serum and urine creatinine were measured using the Jaffe assay and urine albumin using an immunoturbidity method implemented on an automated chemistry analyzer (Hitachi 911, Roche Diagnostics, Indianapolis, IN). Serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride concentrations were all measured by standard methodology, also using the Hitachi 911 Chemistry Analyzer. Low-density lipoprotein (LDL) was calculated using the Friedewald equation when the triglyceride concentration was less than 400 mg/dl.

Exposure

The exposure of interest was self-reported HT use in the last month at the time of the study visit, not including topical vaginal estrogen cream. Participants in Rochester, MN and Jackson, MS brought in pill bottles and medications were recorded by trained study personnel, including the use of specific hormone therapy (estrogen vs. estrogen and progesterone). All participants answered a series of questions regarding their menopausal status, including whether they had reached menopause, whether it was natural, surgical, or due to chemotherapy/radiation, the year or age they reached menopause and whether they had taken or used any pills, skin patches or shots for hormone or estrogen therapy in the last month.

Renal Outcomes

Albuminuria was defined as UACR ≥ 25 mg/g Cr on a spot urine sample, consistent with studies on sex-specific thresholds for albuminuria in women.(17) The estimated glomerular

filtration rate (eGFR) was calculated using the CKD-EPI equation.(18) We defined an abnormal eGFR as < 60 ml/min/1.73 m^2.

Statistical Analysis

We used Fisher's exact test for categorical variables and Wilcoxon rank sum on continuous variables. We fit linear and logistic regression models for the quantitative and categorical measures of renal function that were adjusted for age, race, education, smoking, diabetes, hypertension, RAAS blockers, history of hypertension in either parent, BMI, HDL, LDL, triglycerides, eGFR < 60 ml/min/1.73 m^2, surgical menopause, and age at menopause, all parameters that were significantly different between HT users and non-users. These models were fit with generalized estimating equations to account for sibling relationships in recruitment. Quantitative variables with skewed distributions were log-transformed for all models. We performed a subgroup analysis to evaluate the effect of estrogen vs. estrogen and progesterone therapy in women with medication information.

Materials and Methods: Meta-Analysis

We performed a systematic review and meta-analysis of studies that evaluated the association between HT and albuminuria and/or proteinuria. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement.(19) We included observational studies and randomized control trials (RCTs) of post-menopausal women that compared HT users and non-users, though studies comparing women before and after HT use were also included. HT use could be of any duration and could be determined by self-report, pharmacy records or given as an intervention in a trial. Our outcome of interest was any measure of urinary protein excretion (albuminuria or proteinuria). We did not set any limits on length of follow-up, date of publication, study quality, language, or geographic location.

Data Sources and Search Strategy

We conducted a systemic search of several databases to identify relevant articles. The search strategy was developed in consultation with a PhD statistician with expertise in systematic reviews (NM) and was completed on 2/8/2016. We searched 4 databases (with year of inception): Ovid Medline (1946), Embase (1988), Cochrane Central Register of Controlled Trials (1966) and Scopus (1989) for terms related to estrogen, hormone therapy, menopause, kidney, renal or glomerular function, proteinuria and albuminuria (see Supplement for full search strategy). Two independent reviewers (AK and MG) screened all eligible abstracts and full texts. If the reviewers disagreed on inclusion, the abstract was automatically moved to the next stage of full text review. At the full text stage, disagreement was resolved by consensus and if not possible, by a third reviewer. A data extraction form was developed and included details on study design, study population, inclusion/exclusion criteria, the specific exposure or intervention, the length of follow-up and urinary protein and albumin measures, including continuous and dichotomous variables. If the full text was not in English, we identified two independent reviewers that spoke the relevant language to extract data and assess study quality.

Risk of Bias

Risk of bias was reviewed by two independent reviewers using the Newcastle Ottawa Scale for cohort and case-control studies and the Cochrane Risk of Bias Assessment Tool for RCTs.(20, 21) Each study was given a low, moderate and high quality designation based on the criteria deemed to most important by the investigators. The hierarchy of study methodology using the GRADE approach was then combined with the risk of bias assessments to compare the quality of studies across study designs.(21) For example, a low quality RCT was considered comparable to a high quality observational study.

Missing Data and Subgroup Analyses

Certain variables were imputed based on the techniques given in the Cochrane Handbook of Systematic Reviews of Interventions.(21) Subgroup analyses determined *a priori* included standardized mean difference (SMD) by study type (observational vs. RCTs), the inclusion vs. exclusion of women with diabetes, type of outcome reported (albuminuria vs. proteinuria), estrogen vs. estrogen and progesterone combined HT, and quality. To further explore the reasons for different outcomes, we also evaluated the SMD in observational studies by study type (prospective cohort versus cross-sectional analysis and case-control studies).

Publication Bias

We did not make a funnel plot to evaluate for publication bias, given the small number of studies and our concern that the difference in results between our small and large studies may be the result of study heterogeneity.(22)

Statistical Analysis

The main outcomes of interest were the association of HT use and elevated proteinuria or albuminuria (odds ratio (OR)) or the difference in mean albuminuria or proteinuria associated with HT use. Priority was given to measures adjusted for age and diabetes. Dichotomous and continuous measures of association were converted to SMDs to estimate an effect size for each study. If a study reported both dichotomous and continuous measures, the most appropriately adjusted outcome was preferentially taken. Random effects models were used for to pool the SMDs. Heterogeneity was assessed using the I^2 statistic. All analyses were performed with Review Manager, Version 5.

Results: GENOA

Baseline Characteristics

The demographics and medical history of HT users and non-users are shown in Table 1. HT users were significantly younger, more likely to smoke and differed in race/ethnic distribution and level of education. They were less likely to have diabetes, had lower BMI, LDL and triglycerides and higher HDL in serum. The mean (standard deviation (SD)) age at menopause in the cohort was 45.5 (7.2) years. Half of the women reported that onset of menopause was natural (50.9%) and half was surgical (48.9%), with only 4 women reporting menopause due to chemotherapy (n=2), radiation (n=1) or other causes (n=1). In the group

of women who reported natural menopause, the mean (SD) age at menopause was 49.1 (5.4) vs. 39.7 (6.9) in those women with surgical menopause. Women who were on HT had an earlier age at menopause and were more likely to have surgical menopause.

Renal Outcomes

The unadjusted renal parameters in HT users and non-users are shown in Table 2. UACR was significantly lower in those on HT versus those who were not (3.3 vs. 5.2 mg/g Cr, $p<0.001$). The proportion of women with albuminuria (9.2% vs. 19.0%) and eGFR < 60 ml/min/1.73 m^2 (6.1% vs. 10.7%) was significantly lower in HT users as compared to non-users.

HT users had a decreased odds of having microalbuminuria after adjusting age alone (OR 0.44, 95% CI 0.32-0.66). After further adjusting for race, education, smoking, diabetes, hypertension, history of hypertension in either parent, BMI, HDL, LDL, triglycerides, use of RAAS blockers, eGFR < 60 ml/min/1.73 m^2, surgical menopause and age at menopause, HT users had a decreased odds of having albuminuria (adjusted OR 0.65, 95% CI 0.45-0.95). The odds of having eGFR < 60 ml/min/1.73 m^2 was no longer significantly different between the groups after adjustment (adjusted OR 0.74, 95%CI 0.48- 1.14).

In our subgroup analysis of women in GENOA who provided pill bottles (n=1468), 494 women were on HT, of which 362 were on estrogen alone and 102 were on estrogen and progesterone, with the 30 remaining women on other HT combinations (progesterone alone, estrogen and testosterone, etc.). The majority of the 477 women taking estrogen were on conjugated estrogens (n=391, 82.1%) via the oral route (n=412, 86.4%). We found that estrogen alone was significantly associated with a decreased odds of albuminuria (OR 0.63, 95% CI 0.41- 0.96) after adjustment. Estrogen and progesterone therapy was associated with a greater decrease in odds of albuminuria, but this was not significant (OR 0.25, 95% CI: 0.06-1.09).

Results: Meta-Analysis

Description of included studies

We identified 1088 abstracts for screening and 945 were excluded at the abstract phase (Figure 1). Twelve studies, including our own, were included in the qualitative and quantitative synthesis. The kappa statistic for agreement on inclusion between the reviewers was 0.95 (95% CI 0.86-1.00). Table 3 shows the details of the study designs of included studies. There were 3 RCTs and 9 observational studies. The RCTS were all placebo-controlled and of similar size, with approximately 30 women in each arm. The observational studies included several large cohort studies –including the Nurse's Health Study (NHS) and the Insulin Resistance and Atherosclerosis Study (IRAS).(11, 12) There were two population-based cohort studies – the Rancho Bernando study from a suburban community in Southern California and the Prevention of Renal and End-Stage Disease (PREVEND) cohort from Groningen, Netherlands that was recruited to identify the presence of elevated urine albumin excretion in the population.(9, 10) There were 2 small, uncontrolled, interventional studies where women were given hormone therapy and observed before and

after therapy.(23, 24) Overall, there were 8,343 women included in all of the studies. The risk of bias assessments, study quality within each study design category and across study designs are shown in Table 4.

Meta-Analysis

The individual outcomes, units of measure, threshold for an 'abnormal' dichotomous variable and adjustments made to the outcomes are shown in Table 5. The forest plot of all included studies is shown in Figure 2. Twelve studies were included in meta-analysis; 9 were observational studies and 3 were RCTS. The SMD of the effect of HT on urine proteinuria/albuminuria in the RCTs was 0.02 (95% CI -0.29–0.33, p = 0.89) and -0.13 (95% CI -0.31-0.05, p=0.15) in the observational studies. Nine studies reported albuminuria, while 3 studies reported proteinuria as an outcome (Figure 3). All three RCT studies reported albuminuria as outcome. The studies that reported albuminuria showed a significant effect in the direction of benefit of HT (-0.15, 95% CI -0.27- -0.04), whereas there was no net effect in the studies that reported proteinuria (-0.37, 95% CI -1.46-0.73). The effect was no longer significant in a sensitivity analysis excluding our own study. The overall pooled estimate of all studies was -0.11 (95% CI -0.27-0.05) consistent with a small, non-significant effect in the direction of benefit of HT. The heterogeneity of the overall effect was high (I^2 = 75%).

In a sensitivity analysis, we removed the two studies with no comparator group (23, 24) and the overall pooled estimate was significant at -0.15 (95% CI -0.26- -0.04). No statistically significant difference was observed in any other predefined subgroup analyses (study quality, inclusion/exclusion of diabetics or estrogen vs. estrogen/progesterone). In a sensitivity analysis of observational studies, we pooled only estimates from the 5 studies, including our own (9-12), that were adjusted for important covariates, such as age, diabetes and hypertension (Table 5) and found a significant benefit in the direction of HT (-0.21, 95% CI -0.34 - -0.08). In our analysis of observational study types, we found that cross-sectional and case-control studies (9-11, 25), including our own, had an SMD of -0.06 (95% CI -0.19 – 0.06) for the association of HT use and albuminuria, whereas prospective, cohort studies had a significant SMD of -0.26 (95% CI -0.53 – 0.0). Of note, both Fung and Agarwal *et al* (10, 11) presented cross-sectional and prospective, cohort analyses and so the results from each portion of these two studies were considered separately in this subgroup analysis and we did not test for interaction as the studies were not independent observations.

Discussion

The association of HT and albuminuria was evaluated in a large, racially and ethnically diverse cohort with well-defined medical co-morbidities. We found that HT use was significantly associated with a 40% decreased odds of albuminuria after accounting for traditional risk factors for chronic kidney disease. We next conducted a systematic review and meta-analysis and identified a heterogeneous body of evidence on the association of HT and urine protein excretion. The overall pooled estimate on the association of HT use and measures of albuminuria or proteinuria was small and not significant, but became significant in the direction of benefit when including only studies that evaluated albuminuria, a more sensitive marker of glomerular permeability, and if the studies with no comparator arms

were excluded. We also found a significant benefit in prospective cohort studies, but not in case-control and cross-sectional analyses, nor in randomized controlled trials. After synthesizing our data with the available literature and evaluating the potential causes for heterogeneity, we feel that the association between hormone therapy and reduced albuminuria is truly present and may be due to the biologic effects of estrogen, issues of study design and confounding, or a combination of both.

The rationale behind studying the effect of estrogen on kidney function has come from several different arenas. In experimental methods where one can manipulate the sex hormones separately, estrogen appears to be renoprotective.(8, 26, 27) From a clinical perspective, women have demonstrated slower progression of chronic kidney disease, as was shown in a meta-analysis of 11,345 participantss with non-diabetic renal disease.(28) In the Modification of Diet in Renal Disease study, a post-hoc analysis showed that the decline in eGFR was slower in women than men under the age of 52, but similar after the age of 52, though this effect was lost after multivariate analysis taking into account blood pressure, urine protein measurements and HDL.(2) It is possible that HT use is reducing albuminuria indirectly, such as through effects on blood pressure, as opposed to a direct effect on kidney function. While the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial did not show any significant effects of conjugated equine estrogen on blood pressure over a 3-year period (29), a study on women undergoing oophorectomy found that there is a significant increase in mean 24-hour blood pressure, night-time blood pressures and forearm vascular resistance immediately after removal of the ovaries that improves after 3 months with transdermal estradiol, suggesting that estrogen is important for blood pressure homeostasis. (30)

Studies on HT use in post-menopausal women have been initiated as a way to understand the effect of estrogen on human kidneys. We identified 9 observational studies, including our own, that have specifically studied this relationship. We found that the effect size of approximately a 40% reduction in the odds of albuminuria was consistent across 3 three observational studies of similar design.(11, 12) The observational study by Fung *et al*, reported an adjusted odds ratio from the cross-sectional portion of the study which suggested an increased risk of albuminuria, but found that HT use was associated with a decline in albuminuria as a continuous measure in the longitudinal portion of the study.(10) This difference may reflect a survivor bias, whereby the women who survived the prospective portion of the study were younger and healthier. Another outlier in the observational study group is the study by Monster *et al*.(9) This study differed from the others in that it was a population-based, nested case-control study. The three small RCTs showed overall no effect of HT on albuminuria in a 6-month time frame.(31-33) The consistency of the effect size in a subset of observational studies that differs from other observational studies and RCTs suggest the presence of a systematic bias.

One potential source of bias could be the healthy user bias, which is well described in the literature on HT and cardiovascular disease.(34) The NHS and a large systematic review of observational studies both demonstrated a reduced risk of coronary heart disease in HT users,(35, 36) while two large RCTs, the Heart and Estrogen-progestin Replacement Study and the Women's Health Initiative (WHI), demonstrated an increased risk of cardiovascular

disease in HT users.(37, 38) The healthy user bias suggests that women who take HT are fundamentally different than women who do not and that those differences are strongly associated with decreased cardiovascular risk, or in our case, a decreased risk of albuminuria. HT use in our cohort was not only associated with a more favorable metabolic profile, but also race and level of education. Despite adjustment for these confounders, there is still a risk for residual confounding, particularly for socioeconomic factors, which play a significant role in disease.(39)

An important factor we could not address in our study is when in relation to menopause HT was started, which has been shown to be an important consideration.(40) In the NHS, the women on HT for the longest (> 15 years), underwent menopause at the youngest age and had the largest decrease in risk of albuminuria.(12) A study by Ahmed *et al* demonstrated a larger decline in eGFR in HT users as compared to non-users in an elderly population, which could reflect the importance of woman's age on the effects of HT.(41)

Our study has several limitations. We had no information on how long women were taking HT and did not have longitudinal measurements of renal function. The study visit in GENOA relied heavily on self-report by survey, however, we were able to confirm HT use in a subset of women that had their pill bottles reviewed (n=1468) and found that self-report of hormone use was accurate in 96.6% of cases. Blood pressure and lipid measurements were taken directly as part of the study, as well. As the majority of women were on oral conjugated estrogens, these results may not be applicable to women on other formulations, such as transdermal bioidentical hormones. The participants in the GENOA study were recruited on the basis of hypertension and/or diabetes and so this may limit the generalizability of the results. We tried to address these limitations by putting our study in the context of a systematic review. We had to impute several values for the meta-analysis, but we used conservative estimates and sensitivity analyses to ensure that our assumptions were not affecting our results. The overall quality of the evidence is low to moderate. While we were able to find a statistically significant association between HT use and albuminuria, the clinical significance of this finding is unclear.

Conclusion

While the biologic basis for estrogen having a potentially beneficial effect on renal function is strong, the results in human studies are mixed. We found that HT was associated with a reduced risk of albuminuria, consistent with the results of other observational studies of a similar design. In our meta-analysis, we found that studies evaluating specifically albuminuria, as opposed to total proteinuria, showed a net benefit of HT. Additional physiologic studies in humans are needed to further elucidate the effects of sex hormones on renal function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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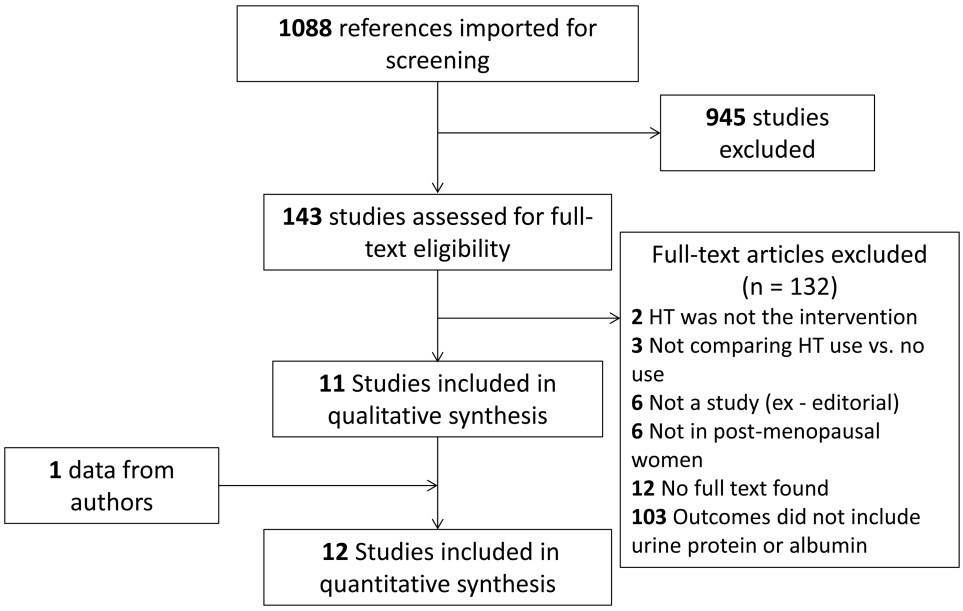

Figure 1.

Flow diagram outlining the identification of studies included in the systematic review and meta-analysis. HT = Hormone Therapy.

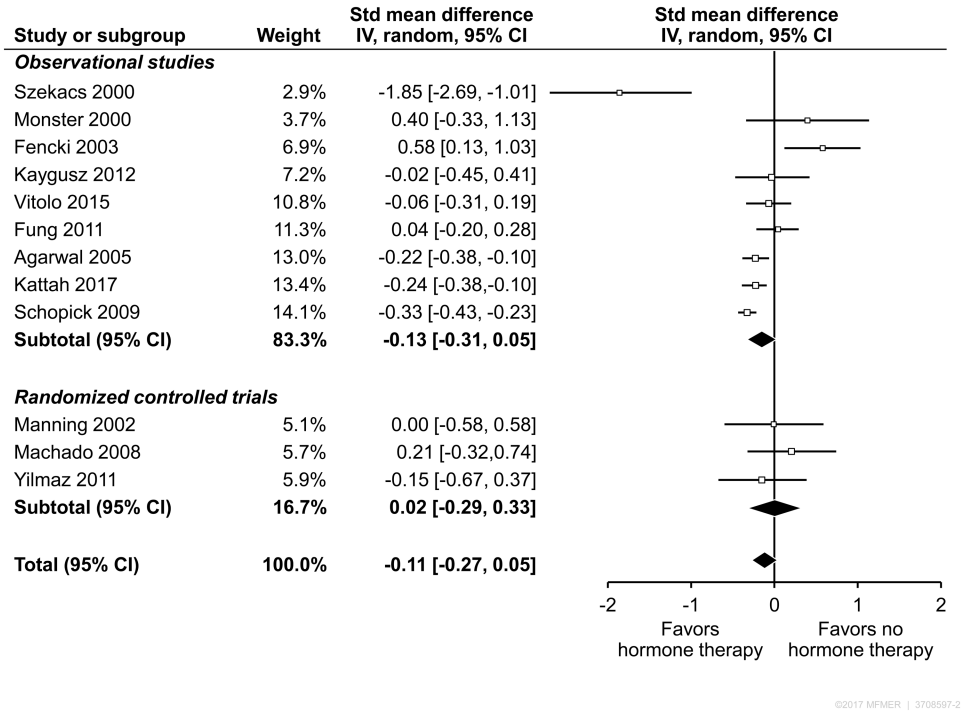

Figure 2.

Forest Plot of the standardized mean difference of the effect of hormone therapy on urine albuminuria/proteinuria in observational studies and randomized controlled trials. Each study is listed according to subgroup, with the corresponding weight, standardized mean difference and 95% Confidence Interval (CI).

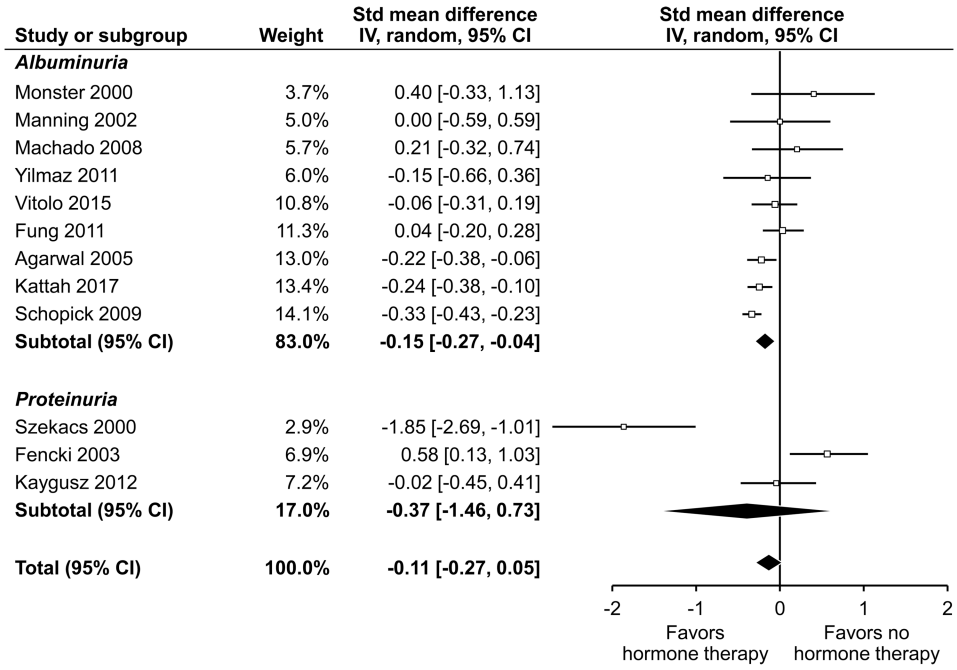

Figure 3.

Forest Plot of the standardized mean difference of the effect of hormone therapy on urine albuminuria and proteinuria in all included studies. Each study is listed according to subgroup, with the corresponding weight, standardized mean difference and 95% Confidence Interval (CI).

Table 1

Participant Demographics, Medical History and Unadjusted Renal Parameters in Hormone Therapy Users and Non-users.

Characteristic[a]	HT users (n=574)	HT non-users (n=1462)	p-value
Age, mean (SD)	60.6 (7.5)	63.3 (8.8)	<0.001[b]
Race, n(%)			<0.001[c]
Non-Hispanic White	255 (44.4%)	253 (17.3%)	
Hispanic	80 (13.9%)	488 (33.4%)	
Non-Hispanic Black	239 (41.6%)	721 (49.3%)	
Education, n(%)			<0.001[c]
Less than High School	66 (11.5%)	441 (30.1%)	
Partial High School	23 (4.0%)	63 (4.3%)	
High School Graduate/GED	204 (35.6%)	396 (27.1%)	
Post High School Education	281 (49.9%)	562 (38.4%)	
Smoking, n(%)	202 (35.2%)	417 (28.5%)	0.004[c]
Hypertension, n(%)	442 (77.1%)	1114 (76.3%)	0.73[c]
Diabetes, n(%)	117 (20.4%)	610 (41.7%)	<0.001[c]
BMI	30.6 (26.4,35.3)	31.7 (27.7, 36.6)	<0.001[d]
Surgical Menopause, n(%)	330 (69.1%)	456 (45.9%)	<0.001[c]
Age at menopause, median (IQR)	45 (39-50)	47 (40-51)	<0.001[d]
Total cholesterol (mg/dl)	202.2 (175.9, 228)	200.5 (175,229.6)	0.93[d]
LDL (mg/dl)	112.8 (90.7, 140.1)	123.5 (97.0, 149.3)	<0.001[d]
Triglycerides (mg/dl)	138.5 (95, 193)	123 (89, 175.6)	<0.001[d]
HDL (md/dl)	57.8 (49.9, 70.6)	52.3 (43.5, 62.8)	<0.001[d]
HTN in either parent, n(%)	445 (77.5%)	1011 (69.1%)	<0.001[c]
Diabetes in either parent, n(%)	170 (35.6%)	347 (35.0%)	0.86[c]
UACR (mg/g Cr)	3.3 (1.5, 6.7)	5.2 (2.2, 16.2)	<0.001[d]
UACR >25 mg/g Cr, n(%)	53 (9.2%)	287 (19.0%)	<0.001[c]
Cr (mg/dl)	0.75 (0.66, 0.86)	0.75 (0.65, 0.89)	0.28[d]
eGFR (ml/min/1.73m^2)	91.4 (78.5, 101.7)	89.7 (74.2, 101.5)	0.05[d]

Characteristic[a]	HT users (n=574)	HT non-users (n=1462)	p-value
eGFR< 60 ml/min/1.73m^2, n(%)	35 (6.1%)	156 (10.7%)	0.001[c]

Abbreviations: GED = General Education Diploma, HT = hormone therapy, BMI = body-mass index, HDL = high density lipoprotein, LDL = low density lipoprotein, HTN = hypertension, UACR = urinary albumin-to-creatinine ratio, Cr = creatinine, eGFR = estimated glomerular filtration rate, BSA = body-surface area.

[a] All data presented as n(%) and median (interquartile range) unless otherwise specified.

[b] Student's t-test as variable was normally distributed.

[c] Fisher's Exact Test

[d] Wilcoxon Rank Sum.

Table 2

Logistic Regression Model for urinary albumin-to-creatinine ratio > 25 mg/g Cr in Hormone Therapy users vs. Non-users (n=2036) GENOA all - Non-Hispanic White and Black and Hispanic

Parameter	Odds Ratio	95% Confidence Interval	p-value
HT use vs. no use[a]	0.65	0.45-0.95	0.02
Age, per 10 years	0.92	0.78-1.09	0.35
Race			
Non-Hispanic White	Ref	--	--
Non-Hispanic Black	5.02	3.08-8.18	<0.001
Hispanic	2.25	1.31-3.85	0.003
Education			
Post High School Education	Ref	--	--
High School Graduate or GED or less	1.61	1.15-2.25	0.006
Diabetes	3.89	2.86-5.29	<0.001
Hypertension	2.67	1.74-4.10	<0.001
Log(BMI)	1.36	0.29-6.38	0.70
Smoking	0.85	0.63-1.15	0.3
Log(Triglycerides)	5.34	2.55-11.18	<0.001
Log(HDL)	3.79	1.09-13.12	0.04
Log(LDL)	1.51	0.59-3.90	0.39
HTN in either parent	1.04	0.78-1.39	0.78
RAAS blockers	0.75	0.56-1.01	0.06
eGFR< 60 ml/min/1.73 m^2	3.46	2.38-4.98	<0.001
Surgical menopause	0.76	0.55-1.04	0.09
Age at menopause	0.99	0.97-1.01	0.16

Abbreviations: GED = General Education Diploma, HT = hormone therapy, BMI = body-mass index, HDL = high density lipoprotein, LDL = low density lipoprotein, HTN = hypertension, RAAS = renin-angiotensin-aldosterone system blockers, eGFR =estimated glomerular filtration rate

[a]Adjusted value for age, race, education, smoking, diabetes, hypertension, hypertension in either parent, BMI, HDL, LDL, triglycerides, RAAS blockers, eGFR< 60 ml/min/1.73 m^2, surgical menopause (vs. other including natural, chemotherapy and other unspecified causes), and age at menopause.

Table 3

Full text articles included in systematic review and meta-analysis.

Study	Design	Relevant Inclusion/Exclusion Criteria	Intervention or Exposure	Sample Size	Average Age of Women in each group	Length of intervention or exposure
Manning 2002(32)	Randomized Controlled Trial	Type II DM included, but poor control and HbA1C > 10% excluded	Conjugated equine estrogens 0.625 mg/day and medroxyprogesterone acetate 2 mg/day (oral) vs. placebo	HT – 29 Placebo - 32	HT – 62 Placebo – 65	6 months
Machado 2008(30)	Randomized Controlled Trial	Age 40-60, exclude fasting glucose > 100 mg/dl	Estradiol 1 mg/day, oral vs. placebo	HT – 30 Placebo – 30	HT – 51.0 Placebo – 51.1	6 months
Yilmaz 2011(31)	Randomized Controlled Trial	Women after oophorectomy, DM, HTN and renal disease excluded	Estradiol 50 μg/day, transdermal OR conjugated equine estrogens 0.625 mg/day vs. placebo	HT – 30 Placebo – 28	Not given	6 months
Szekac 2000(24)	Observational cohort	Included only women with diabetic nephropathy (250-750 mg protein/24 hours)	Estradiol 2 mg/day and norgestrel 0.5 mg/day (oral)	HT – 16 No comparator	HT – 51.9	14 weeks
Monster 2000(9)	Observational – case-control	Included only women with microalbuminuria, age 25-75 (PREVEND, population-based cohort)	Current use of HT in last year by pharmacy records	HT – 198 No HT – 1245	HT – 60.4 No HT – 58.1	Duration of use < and > 5 years reported
Fencki 2003(23)	Observational cohort	Included women with DM for 2 years and women with HTN	Estradiol 0.5 mg and norethisterone acetate 0.25 mg/day (transdermal)	HT and DM – 20 HT and HTN - 21	HT and DM – 50.9 HT and HTN – 52.6	12 weeks
Agarwal 2005(11)	Observational – cross-sectional and prospective	Various glucose tolerances (Insulin Resistance Atherosclerosis Study)	Current use of HT	Post-menopausal women at beginning of study – 744	HT – 57 No HT - 58	Average length of HT – 8 years
Schopick 2009(12)	Observational cohort	Excluded DM and macroalbuminuria (>355 mg/g Cr) (Nurse's Health Study)	Current or past use of HT	Current HT = 1127 Past Use = 574 No Current HT = 499	Current HT – 65.6 No HT – 67.7	Duration of use reported up to > 15 years
Fung 2011(10)	Observational – cross-sectional and prospective	Excluded residents with unknown menopausal and HT status (Rancho Bernardo Study, population-based cohort)	Current or past use of HT	Post-menopausal women at beginning of study – 1044	HT – 63.7 No HT – 68.8	Past users – 7.9 years and Current users – 16.5 years
Kaygusz 2012(41)	Observational cohort	DM and HTN excluded	Estradiol hemihydrate 1.03 mg/day and norethisterone acetate 0.5 mg/day vs. control	HT – 35 No HT – 50	HT – 52 No HT – 53.2	At least 1 year prior to study
Vitolo 2015(42)	Observational, cross-sectional	Normal albumin excretion 6 months prior to the study	Estrogen-containing HT	Post-menopausal women at	HT – 54.4 No HT – 55.6	Within the last year

Study	Design	Relevant Inclusion/Exclusion Criteria	Intervention or Exposure	Sample Size	Average Age of Women in each group	Length of intervention or exposure
				beginning of study = 374		

Abbreviations – HT, hormone therapy, DM, Diabetes Mellitus, HTN, hypertension

Table 4

Risk of Bias Assessments and Study Quality.

Study	Study Design/Risk of Bias Scale	Main Source of Risk of Bias	Quality[a] within study design category	Quality[a] across study designs
Manning 2002(32)	Randomized Controlled Trial/Cochrane Risk of Bias Tool	Incomplete Outcome Data, selective outcome reporting, significant baseline imbalance	Low	Moderate
Machado 2008(30)	Randomized Controlled Trial/Cochrane Risk of Bias Tool	Low risk of bias	High	High
Yilmaz 2011(31)	Randomized Controlled Trial/Cochrane Risk of Bias Tool	No description of randomization, allocation concealment or blinding	Moderate	High
Szekac 2000(24)	Observational Study/Newcastle-Ottawa Scale, Cohort study	Low risk of bias	High	Moderate
Monster 2000(9)	Observational Study/Newcastle-Ottawa Scale, Case-Control study	Low risk of bias	High	Moderate
Fencki 2003(23)	Observational Study/Newcastle-Ottawa Scale, Cohort study	Low risk of bias	High	Moderate
Agarwal 2005(11)	Observational Study/Newcastle-Ottawa Scale, Cohort study	Low risk of bias	High	Moderate
Schopick 2009(12)	Observational Study/Newcastle-Ottawa Scale, Cohort study	Ensuring outcome was not present at beginning	Moderate	Low
Fung 2011(10)	Observational Study/Newcastle-Ottawa Scale, Cohort study	Low risk of bias	High	Moderate
Kaygusz 2012(41)	Observational Study/Newcastle-Ottawa Scale, Cohort study	Minimal description of cohort, did not ensure outcome was not present at beginning	Low	Very low
Vitolo 2015(42)	Observational Study/Newcastle-Ottawa Scale, Cohort study	Minimal description of cohort and exposure	Low	Very low
Manning 2002(32)	Observational Study/Newcastle-Ottawa Scale, Cohort study	Ensuring outcome was not present at beginning	Moderate	Low

[a]Each study was given a very low, low, moderate or high quality designation based on the risk of bias (Newcastle-Ottawa Scale for observational studies and Cochrane Risk of Bias Assessment for Randomized Controlled Trials) and the hierarchy of study methodology

Table 5

Outcomes Reported for Individual Studies.

Study	Outcome	Threshold	Main Outcome used in Meta-Analysis	Value of Outcome	Adjustments
Manning 2002(32)	Albumin-to-creatinine ratio (mg/g Cr)	30 mg/g Cr	Median (IQR) range of change from baseline to end of intervention	Median (IQR) of change[a] HT: 2 (-11, 21) Placebo: 2 (-1, 14)	None
Machado 2008(30)	Urine albumin excretion (μg/min) by 12 hour collection	N/A	Mean change in microalbuminuria from baseline to follow-up	Mean (SD) of change HT: -0.16 (2.79) Placebo: -0.86 (3.64)	None
Yilmaz 2011(31)	Microalbumin (mg/L)	N/A	Mean change in microalbuminuria from baseline to follow-up	Mean (SD imputed)[b] of change HT: -11.5 (24.3) Placebo: -8.2 (18.3)	None
Szekac 2000(24)	24-hour urine protein (mg/24 hrs)	N/A	Mean change in proteinuria from baseline to follow-up	Mean (SD) of pre- and post-HT Pre-HT: 452(39) Post-HT: 370 (47)	None
Monster 2000(9)	Microalbuminuria	30-300 mg/g Cr	Odds Ratio – adjusted	OR (95% CI): 2.05 (1.12-3.77)	Age, HTN, DM, obesity, hyperlipidemia, smoking
Fencki 2003(23)	24-hour urine protein (mg/24 hrs)	N/A	Mean change in proteinuria from baseline to follow-up (combined HT and DM)	Mean (SD) of pre- and post-HT Pre-HT: 125.9 (31.9) Post-HT: 142 (21.3)	None
Agarwal 2005(11)	Albumin-to-creatinine ratio (mg/g Cr)	25 mg/g Cr	Odds Ratio – adjusted	OR (95% CI): Prospective: OR 0.67 (0.43-1.01) Mean (SD) of ln (UACR) HT: 2.16 (0.82) No HT: 2.43 (1.07)	Age, race, DM, SBP, DBP, triglycerides, HDL, smoking, BMI, GFR
Schopick 2009(12)	Top albumin-to-creatinine ratio decile	9.2 mg/g Cr	Odds Ratio – adjusted	OR (95% CI): 0.55 (0.39-0.77) Median (IQR) of two groups: HT (> 6 years): 2.58 (1.6-4.6)[c] No HT: 3.5 (2.1-5.8)	Age, BMI, hypertension and eGFR
Fung 2011(10)	Albumin-to-creatinine ratio (mg/g Cr)	25 mg/g Cr	Odds Ratio - adjusted	Cross-sectional: OR 1.07 (0.73-1.56) Prospective: Mean (SD imputed)[b] change of ln(UACR) HT: -0.07 (0.8) No HT: 0.31 (0.77)	Age, weight, DM, smoking, hyperlipidemic, HTN Age
Kaygusz 2012(41)	Protein-to-creatinine ratio	N/A	Difference in mean between HT and no HT group	Median (IQR) of two groups[a]: HT: 0.08 (0.01-0.97) No HT: 0.09 (0-0.6)	None
Vitolo 2015(42)	Albumin-to-creatinine ratio (mg/g Cr)	N/A	Odds Ratio – unadjusted	OR (95% CI): 0.90 (0.549-1.479) Median (IQR) of two groups[a]:	None

Study	Outcome	Threshold	Main Outcome used in Meta-Analysis	Value of Outcome	Adjustments
				HT: 6.45 (2.16-29.1) No HT: 6.15 (2.70-33.9)	

[a] Median taken as mean change and interquartile range converted to standard deviation of change for analysis of continuous outcomes.

[b] Standard deviation of change imputed using the correlation coefficient calculated from Machado *et al* (correlation coefficient = 0.53).

[c] Combined medians of all groups with > 6 years of hormone therapy and took widest confidence interval for the group.

Abbreviations: Cr = creatinine, IQR = interquartile range, HT = hormone therapy, SD = standard deviation, N/A = not applicable, HTN = hypertension, DM = diabetes, BMI = body-mass index, OR = odds ratio, CI = confidence interval, UACR = urine albumin-to-creatinine ratio