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Endogenous Sex Hormones and Glucose Tolerance Status in Postmenopausal Women

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Context: In postmenopausal women, endogenous estradiol (E2) and free testosterone (T) have been positively associated with glucose intolerance and type 2 diabetes. Most studies have not examined these associations in a large group of postmenopausal women.

Objective: The objective was to examine the association between endogenous sex hormones and glucose tolerance in postmenopausal women.

Design, Setting, and Participants: This was a cross-sectional study of 1973 postmenopausal women ages 45–84 yr, not taking hormone replacement therapy, in the Multi-Ethnic Study of Atherosclerosis baseline examination.

Main Outcome Measures: Impaired fasting glucose (IFG) and diabetes were defined based on fasting blood sugar and/or treatment for diabetes. In women with normal glucose tolerance, insulin resistance was estimated using homeostasis model assessment of insulin resistance (HOMA-IR).

Results: Increasing quartiles of bioavailable T and E2 and decreasing quartiles of SHBG were associated with significantly increased odds of IFG and diabetes (all P for trend < 0.001). Except for the association of bioavailable T with diabetes, the other associations persisted after multivariable adjustment. Although higher dehydroepiandrostenedione (DHEA) was associated with greater odds of IFG (P for trend = 0.02), it was not associated with diabetes. Of 1100 women with normal glucose tolerance, E2 and DHEA were positively associated, and SHBG was inversely associated with HOMA-IR (all $P < 0.001$) after multivariable adjustment. Bioavailable T was associated with HOMA-IR ($P < 0.001$), but not fasting glucose.

Conclusion: Of postmenopausal women, endogenous bioavailable T, E2, and DHEA were positively associated and SHBG was negatively associated with insulin resistance. **(*J Clin Endocrinol Metab* 92: 1289–1295, 2007)**

BOTH ANDROGENS AND estradiol (E2) are associated with diabetes mellitus and altered glucose tolerance. Testosterone (T) given to healthy women leads to impaired glucose metabolism (1–4). Endogenous free T is positively correlated with insulin resistance (5–9), fasting plasma glucose (6, 10, 11), and adiposity (6, 10). Both low levels of SHBG, a marker of hyperandrogenicity (12–14) that is inversely related to insulin (15), adiposity (6, 10), and glucose tolerance (13, 16), and high levels of free T (6), predict the incidence of type 2 diabetes in women. In a recent analysis in the Atherosclerosis Risk in Communities Study, we found that higher free androgen index was associated with the hyperinsulinism and hyperglycemia components of the metabolic syndrome in postmenopausal women (17). However, only having sex hormone data on a select group of women and not on the entire cohort limited this study. The association between dehydroepiandrostenedione (DHEA), another androgen, and glucose tolerance status in postmenopausal women is less clear.

Previous studies have also shown that postmenopausal women with impaired glucose tolerance and type 2 diabetes have higher E2 levels than postmenopausal women with normal glucose tolerance (10, 14, 18). Of healthy postmenopausal women without diabetes or glucose intolerance, E2 was significantly associated with insulin (7) and insulin resistance (19), independent of adiposity. Bioavailable E2 is associated with incident insulin resistance but not with the incidence of type 2 diabetes (6). One study failed to find an association between free E2 and fasting plasma glucose levels (11), and other studies in human and rodent models suggest that E2 may have a beneficial effect on glucose metabolism (20).

Previous studies of premenopausal and perimenopausal women from the Study of Women Across the Nation (SWAN) cohort found that although E2 was not associated with markers of glucose tolerance, free androgen index was positively correlated with glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) (21, 22). To examine further these associations, we determined the relation between endogenous T, E2, SHBG, and DHEA and glucose tolerance status in the Multi-Ethnic Study of Atherosclerosis (MESA). Our study is unique in that it: 1) is one of largest cohort studies with complete ascertainment of sex hormone data on all postmenopausal women; 2) expands on the SWAN Study of premenopausal and perimenopausal women to evaluate associations in an ethnically diverse

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Abbreviations: BMI, Body mass index; CV, coefficient of variation; DHEA, dehydroepiandrostenedione; E2, estradiol; HOMA-IR, homeostatic model assessment of insulin resistance; IFG, impaired fasting glucose; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent; SWAN, Study of Women Across the Nation; T, testosterone.

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group of postmenopausal women; and 3) examined the association between DHEA and glucose tolerance status, which has not been consistently studied in large cohorts.

Subjects and Methods

Study population

MESA is a multicenter, longitudinal cohort study of the prevalence and correlates of subclinical cardiovascular disease and the factors that influence its progression (23). Individuals were excluded if they had clinical cardiovascular disease, including physician-diagnosed angina, stroke, transient ischemic attack, or heart failure, use of nitroglycerine, current atrial fibrillation, or had undergone a procedure related to cardiovascular disease (coronary artery bypass surgery, angioplasty, valve replacement, pacemaker or defibrillator implantation, or any surgery on the heart or arteries) (www.mesa-nhlbi.org). Between July 2000 and August 2002, 6814 men and women who identified themselves as white, Black, Hispanic, or Chinese, and were 45–84 yr of age, were recruited from portions of six U.S. communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. Details on the sampling frames and the cohort examination procedures have been published previously (23). Informed consent was obtained from each participant, and the Institutional Review Boards of each institution approved the study.

Sex hormone levels were measured in 3246 women. Women were excluded from this analysis if they were current users of hormone replacement therapy (n = 1273) or if insulin was their first diabetes treatment medication, indicating the likely presence of type 1 diabetes (n = 17). Thus, the current analyses were based on 1956 postmenopausal women. A woman was considered postmenopausal if she self-reported being postmenopausal, had undergone a prior oophorectomy, and/or was more than 55 yr of age.

Assessment of exposures: endogenous sex hormones

Participants fasted for 12 h and avoided smoking and heavy physical activity for 2 h before each examination. Fasting blood samples were drawn between 0730 and 1030 h. Serum samples, extracted by centrifugation at 2000 × *g* for 15 min or 3000 × *g* for 10 min, were immediately stored at −70 C and shipped to the University of Vermont for long-term freezer storage. Since MESA began, these samples have not been thawed.

Serum hormone concentrations were measured from stored samples in the Sex Hormone Laboratory at the University of Massachusetts Medical Center in Worcester, Massachusetts. Total T and DHEA were measured directly using RIA kits, and SHBG was measured by chemiluminescent enzyme immunometric assay using Immulite kits obtained from Diagnostic Products Corporation (Los Angeles, CA). An ultrasensitive RIA kit from Diagnostic System Laboratories (Webster, TX) was used to measure E2. Percent-free T was calculated according to the method of Södergard *et al.* (47), and free-T concentration was calculated as: [total T × (percent-free T × 0.01)]. Including approximately 5% blind quality control samples in each batch of samples analyzed was performed to monitor assay variability. The quality control serum was obtained from a large pool that was aliquoted into storage vials and labeled identical to MESA participant samples. The overall coefficient of variation (CV) for total T, SHBG, DHEA, and E2 were 12.3, 9.0, 11.2, and 10.5%, respectively.

Assessment of outcomes

Diabetes was defined as a fasting glucose ≥ 7.0 mmol/liter (126 mg/dl) or use of hypoglycemic medication. Impaired fasting glucose (IFG) was defined as a fasting glucose of 5.5–6.9 mmol/liter (range 100–125 mg/dl). Serum glucose was measured by rate reflectance spectrophotometry using thin-film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY) (laboratory CV: 1.1%). Insulin was determined by a RIA method using the Linco Human Insulin Specific RIA Kit (Linco Research, Inc., St. Charles, MO) (lower limit of sensitivity: 2 U/liter; laboratory CV: 4.9%). Insulin resistance was estimated using the HOMA-IR [glucose (mmol/liter)*insulin (mIU/liter)/22.5] because it has been strongly correlated with fasting insulin, and the euglycemic and hyperglycemic clamps (24). HOMA-IR has also predicted type 2 diabetes (25).

Covariates

Self-reported information included sex, age, race/ethnicity, smoking, and prescription medication use. Weight and height were measured using a balance beam and a vertical ruler with participants wearing light clothing and no shoes. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.5 lb. Body mass index (BMI) was calculated as the weight (kilograms) divided by the height squared (meters^2). Waist circumference was measured at the minimum abdominal girth, and the hip circumference was measured at the level of the symphysis pubis and the maximum protrusion of the buttocks. All anthropometric measures were taken in duplicate and averaged. Smoking status was categorized as never, former, or current, and current alcohol use was coded as yes or no. Physical activity was assessed using the MESA Typical Week Physical Activity Survey. The 28-item questionnaire assesses the time and frequency spent in various household, outdoor, sporting, conditioning, and volunteer activities during a typical week in the past month. Moderate and vigorous activities were categorized as low intensity [0–500 metabolic equivalent (MET) min/wk], medium intensity (501–1000 MET min/wk), and high intensity (>1000 MET min/wk).

Analysis

In univariate analyses, median concentrations of each hormone were compared among women with normal glucose tolerance, IFG, and diabetes using the Kruskal-Wallis test because hormone levels were not distributed normally. For the purpose of multivariable analyses, sex hormones were divided into quartiles. Odds ratios and 95% confidence intervals were calculated from multiple logistic regression models to determine the odds of having IFG and diabetes by quartile of each sex hormone, using quartile 1 as the reference. In the multivariable model, adjustment was made for age, race/ethnicity, MESA site, waist circumference, alcohol use, smoking status, and physical activity to examine the independent association between sex hormones and glucose tolerance status. We further adjusted for HOMA-IR in the multivariable model examining the association of sex hormones and SHBG with IFG. Adjustment for HOMA-IR was not made in the models examining the association of sex hormones with diabetes status because diabetes treatment could alter glucose and insulin levels. Linear regression analyses were also performed using log-transformed sex hormone values.

In a second set of univariate analyses excluding women with IFG and treated diabetes, the mean values of fasting glucose and HOMA-IR were estimated for each quartile of each sex hormone. Because HOMA-IR was not normally distributed, it was log-transformed. Multiple linear regression models were used to calculate the mean difference in glucose and mean difference in the natural log of HOMA-IR in each quartile of each sex hormone compared with the lowest quartile. For ease of interpretation, the β coefficients from the HOMA-IR model were exponentiated to values that represented the percent difference in HOMA-IR for each hormone quartile compared with the first quartile. Multivariable adjustment was made for the same covariates as indicated previously. Linear regression analyses were also performed using log-transformed sex hormone values.

Analyses were also stratified by race/ethnicity and BMI (<25 *vs.* ≥25 kg/m^2) to determine whether there were race/ethnicity by hormone or adiposity by hormone interactions. Statistical additive interaction was assessed using likelihood ratio tests of nested linear regression models to determine which model best described the data, in which one model included a term for ethnicity by hormone interaction, and the other model did not. Similar models were constructed and their significance tested for the BMI by hormone interaction. $P < 0.05$ was used to determine statistical significance. Statistical analyses were performed using Stata, version 8.2 (StataCorp, College Station, TX).

Results

Baseline characteristics

Table 1 displays the biological characteristics of postmenopausal women not taking hormone replacement therapy. Chi-

TABLE 1. Baseline characteristics of 1956 postmenopausal women in the MESA not taking hormone replacement therapy

Characteristic[a]	White (n = 587)	Chinese (n = 273)	Black (n = 607)	Hispanic (n = 489)	*P* value for race/ethnicity comparison
Age (yr)	68 (60–74)[b]	66 (58–72)	66 (58–72)	65 (57–72)	0.0001[c]
BMI (kg/m^2)	27.0 (24.1–30.9)	23.9 (21.5–26.2)[d]	30.4 (26.7–35.1)	29.0 (26.0–33.0)	<0.0001[c]
Waist circumference (cm)	96 (85.5–106.4)	87.2 (80.4–94.8)[d]	101 (91.5–112)	99.4 (91.5–109)	<0.0001[c]
Cigarette smoking (%)					
Never	54	96[e]	52	70[e]	<0.0001[f]
Former	35	2.5	32	20.5	
Current	11	1.5	16	9.4	
Moderate + vigorous physical activity in					
0–500 MET min/wk (%)	56	71[g]	48.1[g]	56	
501–1000 MET min/wk (%)	9	4.8	6.8	8	<0.0001[f]
>1000 MET min/wk (%)	35	24.2	45.1	36	
Current alcohol use (%)					
Yes	77[h]	77[h]	53	60	<0.0001[f]
No	23	23	47	40	
Fasting glucose (mmol/liter)[i]	5.17 (4.90–5.50)[b]	5.28 (5.06–5.66)	5.34 (4.95–5.66)	5.28 (5.00–6.16)	<0.0001[c]
Fasting insulin (mIU/liter)[i]	4.8 (3.2–7.3)[h]	4.5 (3.4–6.9)[h]	6.2 (4.0–8.7)	6.2 (4.3–9.3)	<0.0001[c]
HOMA-IR (mmol*mIU/liter^2)[i]	1.12 (0.70–1.73)[h]	1.08 (0.80–1.71)[h]	1.43 (0.90–2.14)	1.45 (0.90–2.31)	<0.0001[c]
% Impaired fasting glucose	25.3[b]	28.4	30.1	29.4	0.001[f]
% Diabetes	6.6[b]	18.2	20.3	19.3	0.001[f]
Endogenous sex hormones					
Total T (nmol/liter)	0.97 (0.66–1.39)	0.80 (0.56–1.18)[d]	1.02 (0.69–1.49)	0.94 (0.59–1.32)	0.0001[j]
Bioavailable T (nmol/liter)	0.24 (0.14–0.38)	0.24 (0.14–0.38)	0.28 (0.17–0.42)[k]	0.24 (0.17–0.42)	0.0002[j]
E2 (nmol/liter)	0.055 (0.0037–0.077)	0.051 (0.037–0.073)	0.066 (0.048–0.092)[k]	0.055 (0.04–0.084)	0.0001[j]
SHBG (nmol/liter)	55 (39.7–75)[b]	48.5 (34.5–68.5)	50.2 (37.5–68.4)	46.4 (33.4–62.3)	0.0001[j]
DHEA (nmol/liter)	10.2 (6.73–14.6)	12.0 (8.78–15.9)[d]	11.0 (7.94–15.3)	11.1 (7.51–15.5)	0.0003[j]

[a] Summary statistics represent median (interquartile range) for continuous variables.
[b] White women were significantly different from all other women.
[c] *P* value generated from ANOVA for race/ethnicity comparison.
[d] Chinese women were significantly different from all other women.
[e] Chinese and Hispanic women were significantly different from white and Black women.
[f] *P* value generated from χ^2 for race/ethnicity comparison.
[g] Chinese and Black women were significantly different from white and Hispanic women.
[h] White and Chinese women were significantly different from Black and Hispanic women.
[i] Summary statistic is given for 1658 women without treated diabetes.
[j] *P* value generated from nonparametric Kruskal-Wallis test for race/ethnicity comparison.
[k] Black women were significantly different from all other women.

nese-American women had significantly lower BMI and waist circumference, and were less likely to be current smokers or be physically active compared with white, Black, and Hispanic women. Black and Hispanic women were the least likely to be current alcohol users. Chinese-American women had similar fasting glucose levels, and prevalence of IFG and diabetes as high-risk Black and Hispanic women, with white women having significantly lower glucose levels and the lowest prevalence of both conditions; however, Chinese women had significantly lower fasting insulin and HOMA-IR. White women had significantly lower fasting insulin and insulin resistance compared with Black and Hispanic women.

Chinese women had significantly lower total T levels and higher DHEA levels compared with the other women. Black women had higher bioavailable T and E2 levels compared with the other women, and white women had the highest SHBG levels. After adjustment for BMI, racial differences in total and bioavailable T and E2 were no longer significant; however, white women had significantly lower DHEA levels, and Chinese and Hispanic women had significantly lower SHBG than Black and white women (data not shown).

Relative odds of IFG and diabetes

Compared with women in the lowest quartile of bioavailable T, those in the highest quartile had greater than 2-fold odds of having IFG and diabetes (Table 2, model 1). Although the association with IFG persisted after multivariable adjustment, the association with diabetes was no longer significant (Table 2, model 2). There was a strong, graded relation between quartiles of E2 and the odds of IFG, with women in the highest quartile of E2 having greater than 3-fold odds of having IFG. The strength of this association was attenuated but remained significant after multivariable adjustment. Similar statistically significant patterns were seen for diabetes (Table 2, model 2).

There were strong, graded inverse associations between SHBG and the odds of IFG and diabetes. Compared with women in the lowest quartile of SHBG, those in the highest quartile had 75% lower odds of having IFG and 81% lower odds of having diabetes (Table 2, model 1). These associations were weaker but remained statistically significant after multivariable adjustment (Table 2, model 2). Finally, although DHEA was associated with significantly greater odds of IFG, it was not associated with greater odds of diabetes. Total T was not associated with IFG or diabetes (data not shown). We found similar associations when we excluded individuals who were taking diabetes medications (insulin, sulfonylureas, thiazolidinediones, and biguanides; data not shown).

In a sensitivity analysis, we sought to determine if the association between sex hormones and SHBG and IFG was medi-

TABLE 2. Relative odds of impaired fasting glucose and diabetes by quartile of each endogenous sex hormone among 1956 postmenopausal women not taking hormone replacement therapy

Quartiles of endogenous hormones	Odds of impaired fasting glucose (n = 558 individuals with impaired fasting glucose; total n = 1658)		Odds of diabetes (n = 297 individuals with diabetes; total n = 1973)	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Bioavailable T				
Q1 (0–0.17) (nmol/liter)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Q2 (0.18–0.24) (nmol/liter)	1.27 (0.93, 1.75)	1.01 (0.68, 1.53)	1.35 (0.90, 2.02)	1.09 (0.62, 1.93)
Q3 (0.25–1.39) (nmol/liter)	1.84 (1.40, 2.42)	1.49 (1.05, 2.11)	1.85 (1.31, 2.40)	1.42 (0.88, 2.28)
Q4 (1.39–18.8) (nmol/liter)	2.32 (1.75, 3.07)	1.78 (1.24, 2.54)	2.05 (1.45, 2.89)	1.45 (0.99, 2.34)
P value for trend	<0.001	0.001	<0.001	0.15
E2				
Q1 (0.009–0.040) (nmol/liter)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Q2 (0.041–0.059) (nmol/liter)	1.48 (1.10, 1.98)	1.14 (0.78, 1.66)	1.45 (0.99, 2.11)	1.62 (0.91, 2.89)
Q3 (0.060–0.081) (nmol/liter)	1.87 (1.38, 2.54)	1.42 (0.97, 2.10)	1.55 (1.05, 2.29)	1.94 (1.10, 3.45)
Q4 (0.082–1.42) (nmol/liter)	3.24 (2.40, 4.37)	2.29 (1.56, 3.35)	2.49 (1.74, 3.57)	2.34 (1.35, 4.05)
P value for trend	<0.001	<0.001	<0.001	0.002
SHBG				
Q1 (11.5–36.5) (nmol/liter)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Q2 (36.6–50.1) (nmol/liter)	0.61 (0.46, 0.82)	0.78 (0.54, 1.12)	0.56 (0.36, 0.70)	0.55 (0.35, 0.86)
Q3 (50.2–69.0) (nmol/liter)	0.47 (0.34, 0.63)	0.61 (0.42, 0.90)	0.38 (0.27, 0.54)	0.52 (0.32, 0.84)
Q4 (69.1–298) (nmol/liter)	0.25 (0.18, 0.34)	0.35 (0.22, 0.53)	0.19 (0.13, 0.29)	0.30 (0.16, 0.54)
P value for trend	<0.001	<0.001	<0.001	<0.001
DHEA				
Q1 (0.52–7.56) (nmol/liter)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Q2 (7.57–11.0) (nmol/liter)	1.13 (0.84, 1.54)	1.15 (0.79, 1.69)	0.97 (0.68, 1.39)	0.72 (0.45, 1.17)
Q3 (11.1–15.3) (nmol/liter)	1.86 (1.38, 2.52)	1.86 (1.27, 2.72)	1.06 (0.74, 1.52)	0.77 (0.47, 1.26)
Q4 (15.4–52.7) (nmol/liter)	1.68 (1.23, 2.29)	1.43 (0.97, 2.13)	1.13 (0.78, 1.64)	0.77 (0.47, 1.29)
P value for trend	<0.001	0.02	0.46	0.33

ref, Reference category.

[a] Model 1 is adjusted for age, race/ethnicity, and site.

[b] Model 2 is adjusted for age, race/ethnicity, site, waist circumference, physical activity, alcohol use, cigarette smoking. Waist circumference is adjusted for as a continuous variable.

ated by insulin resistance by further adjusting for HOMA-IR in the multivariable model. The associations of bioavailable T, SHBG, and DHEA with IFG were no longer significant after adjustment for HOMA-IR. There was a trend toward increased odds of IFG with increasing quartiles of E2; however, this association was markedly attenuated (*P* value for trend 0.03).

Association of endogenous sex hormones with fasting glucose and HOMA-IR in women with normal glucose tolerance

In multivariable analyses, E2 and DHEA showed a strong, graded positive association, and SHBG showed a strong, graded, inverse association with fasting glucose and HOMA-IR (Figs. 1 and 2). Although bioavailable T was strongly associated with HOMA-IR, it was not associated with fasting glucose. After multivariable adjustment, percent difference in HOMA-IR was 24% higher among women in the highest quartile of bioavailable T compared with those in the lowest quartile (*P* value for trend < 0.001; Fig. 2). Similar results were seen for the associations between E2 and DHEA, and glucose and HOMA-IR (Figs. 1 and 2). Total T was not associated with fasting glucose or HOMA-IR in univariate or multivariable analyses.

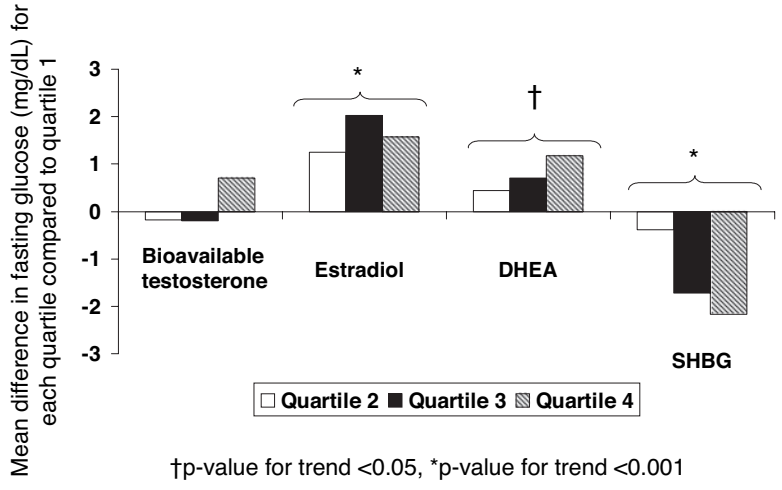
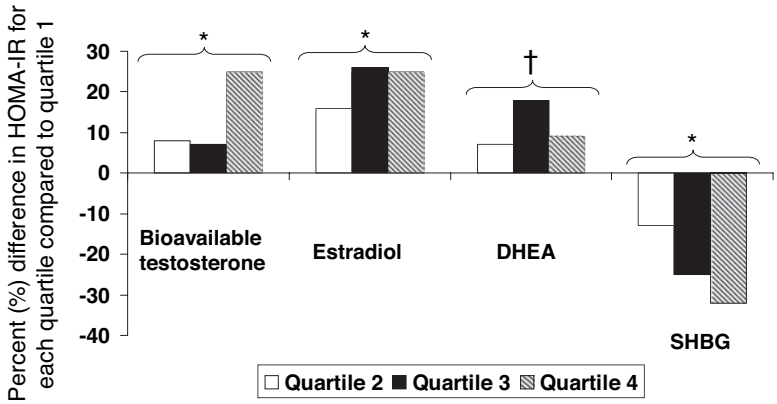


FIG. 1. Mean difference in fasting glucose for each quartile *vs.* quartile 1 of each endogenous sex hormone among 1100 postmenopausal women with normal glucose tolerance not taking hormone replacement therapy, adjusted for age, race/ethnicity, MESA site, waist circumference, physical activity, alcohol intake, and smoking status.



†p-value for trend <0.05, *p-value for trend <0.001

FIG. 2. Percent difference in HOMA-IR for each quartile *vs.* quartile 1 of each endogenous sex hormone among 1100 postmenopausal women with normal glucose tolerance not taking hormone replacement therapy, adjusted for age, race/ethnicity, MESA site, waist circumference, physical activity, alcohol intake, and smoking status.

SHBG showed a strong inverse association with mean fasting glucose and percent difference in HOMA-IR, which were 0.12 mmol/liter and 23% lower, respectively, among women in the highest quartile of SHBG compared with those in the lowest quartile in multivariable analysis (P value for trend < 0.001; Figs. 1 and 2).

Additional exploratory analyses and assessment for interaction

When linear regression analyses were conducted using log-transformed hormone values as continuous variables, our results were identical to those obtained when sex hormones were modeled as quartiles (data not shown). No interaction was seen between sex hormones and BMI or between sex hormones and race/ethnicity with regard to glucose tolerance status or measures of insulin resistance.

Discussion

We found that among postmenopausal women not taking hormone replacement therapy, higher levels of bioavailable T were associated with greater odds of having IFG, but it was not associated with diabetes in multivariable analyses. Higher levels of E2 and lower levels of SHBG were strongly associated with greater odds of having both IFG and diabetes. There was a trend toward higher levels of DHEA being associated with greater odds of having IFG, but it was not associated with diabetes. These associations persisted after multivariable adjustment; however, adding HOMA-IR to the model explained all of the associations of sex hormones and SHBG with IFG. In a subsidiary analysis of postmenopausal women with normal glucose tolerance, bioavailable T was positively associated with HOMA-IR; however, it was not associated with fasting glucose. E2 and DHEA were positively associated, and SHBG was negatively associated with both fasting glucose and HOMA-IR in multivariable analyses.

In women with normal glucose tolerance in MESA, bioavailable T was more strongly associated with our measure of insulin resistance than with fasting glucose. We have previously found that free androgen index was strongly associated with the glucose and insulin components of the metabolic syndrome in postmenopausal women (17). In another cohort, free T has been positively associated with fasting plasma glucose (6, 10, 11), higher fasting and post-challenge insulin levels (6, 7), and higher insulin to glucose ratio (8). Free androgen index has been inversely associated with insulin sensitivity, assessed by the euglycemic-hyperinsulinemia clamp (5). Elevated free T has also predicted incident type 2 diabetes and insulin resistance, independent of age, adiposity, and systolic blood pressure (6). Recently, in the SWAN Study, free androgen index was positively correlated with glucose, insulin, and HOMA-IR, even after adjustment for BMI (22). In short-term clinical trials, androgen administration to healthy women has reduced insulin sensitivity and impaired glucose utilization (1, 4, 26). Antiandrogen therapy given to women with polycystic ovary syndrome and hyperandrogenism has resulted in partial improvement in insulin sensitivity (27, 28) and a decrease in visceral abdominal fat (29). In postmenopausal women, androgen therapy resulted in a gain in visceral abdominal fat, but there was no change in fasting glucose or insulin sensitivity (30). As we recently summarized (17), there are several potential mechanisms by which androgens and glucose metabolism may be associated.

We found that E2 was positively associated with fasting glucose and HOMA-IR, and with IFG and diabetes. Sutton-Tyrrell *et al.* (22) did not find an association between E2 and markers of glucose metabolism in premenopausal and perimenopausal women whose E2 levels were significantly higher than those of the postmenopausal women in our study. Our results may have also differed because the SWAN participants were predominantly Caucasian, with fewer Hispanic and Chinese subjects compared with our MESA population. However, our results are similar to other studies in postmenopausal women showing that impaired glucose tolerance and type 2 diabetes are associated with higher E2 levels than normal glucose tolerance (10, 14, 18). E2 has also been associated with insulin (7) and insulin resistance (19), independent of adiposity, and has predicted incident insulin resistance (6).

The literature regarding the effects of estrogen on glucose metabolism is mixed. Rodent models of E2 deficiency have insulin resistance, and rodent models of type 2 diabetes show that ovariectomy makes female rats susceptible to β-cell destruction (20). These defects are reversed with E2 administration. Several studies have shown that treating healthy women with unopposed E2 or continuous equine estrogen improves

insulin sensitivity and decreases blood glucose (31–34), and among women with diabetes, unopposed E2 (35–37) or combination hormone replacement therapy (38) improves insulin sensitivity and glycemic control. However, although exogenous estrogen administered via hormone replacement therapy was associated with a reduced risk of developing diabetes in postmenopausal women with coronary artery disease (39), pregnancy, a state of high endogenous estrogen, is associated with insulin resistance (26).

Our findings that higher SHBG was associated with better insulin sensitivity confirm those from previous studies (15, 16, 22). Low SHBG has also predicted type 2 diabetes in men and women (12, 14). Insulin is a potent inhibitor of SHBG secretion *in vitro* in hepatoma cells, and, thus, low levels of SHBG may reflect underlying insulin resistance (40). In our study, this is strongly suggested by the association between SHBG and IFG becoming nonsignificant after adjusting for HOMA-IR. Physiologically, SHBG binds T, dihydrotestosterone, and E2 with high affinity, and, thus, regulates their free concentrations, with lower SHBG, reflecting greater androgenicity (41).

In our study we found that DHEA was associated with higher glucose levels, higher HOMA-IR, and increased odds of IFG. DHEA declines significantly with age, and lower levels have been shown cross-sectionally to be associated with diabetes, impaired glucose tolerance, and insulin resistance (26, 42). Administration of DHEA to postmenopausal women resulted in reduction in insulin and glucose levels (43). However, a recent study found that higher DHEA levels were associated with insulin resistance and nonalcoholic fatty liver disease (44). Together, the relation between DHEA and glucose metabolism in postmenopausal women remains unclear and requires further study. In addition, future studies are needed to examine the relation between DHEA-sulfate, a more stable marker of long-term DHEA bioavailability, and glucose tolerance status.

Finally, we found some differences in endogenous sex hormone levels by ethnicity. Chinese women had the lowest total T and highest DHEA levels, and Black women had the highest total and bioavailable T levels and the highest E2 levels in unadjusted analyses. After adjustment for BMI, race/ethnic differences in total and bioavailable T and E2 were no longer significant. In premenopausal and perimenopausal women, Randolph *et al.* (21) similarly found that Chinese women had the highest DHEA-sulfate levels; however, in contrast to our study, T levels were slightly lower in the African-American and Hispanic women. However, in both of our studies, adiposity was an important confounder of the race/ethnic differences in sex hormone levels; they also found that E2 and free T index did not differ by race/ethnicity once BMI was accounted for (21). In another study, Chinese women had lower E2 levels than white women (45). In our study, as in the SWAN Study, the associations between endogenous hormones and glucose metabolism variables were similar for all race/ethnicities (22).

Our study has several strengths. First, we had a large sample size of nearly 2000 postmenopausal women to examine these associations. With the exception of the Rancho-Bernardo Study (6, 10, 11), the majority of other studies have been small. Second, because MESA is an ethnically diverse sample, this allowed us to examine the association between endogenous sex hormones and insulin resistance by race/ethnicity. The SWAN Study is the only other study that we are aware of that has examined these associations in a multiethnic population (22). Third, because individuals with prevalent cardiovascular disease were excluded, this is a healthier, population-based sample, compared with a clinic-based sample. Finally, in contrast to our previous study (17), bioavailable T and other sex hormone measurements were available on the entire cohort of women and not a preselected subset.

Nonetheless, several limitations should be kept in mind in interpreting our data. This was a cross-sectional analysis, which does not allow us to elucidate the temporal association between hormones and glucose parameters; however, the structure of subsequent MESA follow-up examinations will allow for longitudinal analyses in the future. Also, only one measurement of sex hormones was used to characterize each woman's hormonal status; however, it has been previously suggested that a single measure can reliably characterize a person's androgen status (6, 46). We also did not have data on estrone, the primary estrogen present in postmenopausal women.

Our study suggests an association of androgens and estrogens with insulin sensitivity in postmenopausal women. Longitudinal studies are needed to determine the temporal relation between endogenous sex hormones, and the risk of insulin resistance and diabetes. Additional studies are needed to elucidate further the mechanisms by which endogenous sex hormones are related to glucose metabolism and diabetes risk. Finally, studies aimed at altering the endogenous hormonal milieu may have implications for altering glucose metabolism and diabetes risk.

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