Association of Endogenous Sex Hormones With Diabetes and Impaired Fasting Glucose in Men

Multi-Ethnic Study of Atherosclerosis*

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OBJECTIVE — To assess associations of sex hormones with impaired fasting glucose (IFG) and type 2 diabetes in men.

RESEARCH DESIGN AND METHODS — A total of 3,156 African American, Non-Hispanic white, Hispanic, and Chinese-American men aged 45–84 years who participated in the baseline visit of the Multi-Ethnic Study of Atherosclerosis (MESA) were included. Odds ratios and 95% CIs for type 2 diabetes and IFG compared with normal fasting glucose for quartiles of hormones were estimated.

RESULTS — After adjusting for age, ethnicity, BMI, and waist circumference, IFG and diabetes were associated inversely with total testosterone and sex hormone–binding globulin (SHBG) and positively with estradiol (E2). Dehydroepiandrosterone was positively associated with IFG but not with diabetes. Associations did not differ across ethnic groups.

CONCLUSIONS — Regardless of obesity, total testosterone and SHBG were associated inversely and E2 was associated positively with IFG and diabetes in men. Further research is warranted to better understand the underlying biological mechanisms.

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Sex hormones have been associated with type 2 diabetes in men (1,2). Some studies (1,2) have shown that these associations were independent of obesity. In the Third National Health and Nutrition Examination Survey (NHANES III) (2), the only study to include a multiethnic sample, power was insufficient to determine whether associations differed by ethnicity. The population-based Multi-Ethnic Study of Atherosclerosis (MESA), initiated in 2000, provides an opportunity to evaluate cross-sectional associations of sex hormones with both type 2 diabetes and impaired fasting glucose (IFG) in men aged 45–84 years while taking into consideration measures of obesity and ethnicity. Similar analyses examining associations in postmenopausal women (3) were conducted separately because previous research has shown that there is a sex dimorphism in hormone associations with type 2 diabetes (1).

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RESEARCH DESIGN AND METHODS

— Details on the design, recruitment, cohort examination procedures, and methods for blood collection and measurements of sex hormones, serum glucose, and insulin have previously been described (3,4). Information on participant demographic and lifestyle characteristics, medical history, and medication use was collected with standardized questionnaires; height, weight, and waist circumference were measured. BMI was calculated as weight (kilograms)/height (meters squared). All participants gave informed consent, and the MESA protocol was approved by the institutional review board at each participating site.

Of 3,213 men in the MESA cohort, we excluded 49 without sex hormone levels and 8 without fasting glucose measurements, leaving 3,156 participants: 1,243 non-Hispanic white, 388 Chinese, 812 African American, and 713 Hispanic. Men were classified into three groups: diabetes (fasting glucose $\geq$126 mg/dl or current use of diabetes medication), IFG (100 mg/dl $\leq$ fasting glucose $<$ 126 mg/dl), and normal fasting glucose.

Polytomous logistic regression was used to estimate odds ratios (ORs) for quartiles of sex hormones comparing those with diabetes and IFG with those with normal fasting glucose. Analyses were conducted with the ethnic groups pooled, adjusting for ethnicity, and interactions between hormones and ethnicity were tested. Interaction terms were used to obtain ethnicity-specific ORs for quartiles of sex hormones. Covariates included age, BMI, waist circumference, smoking (non-, former, or current smoker), alcohol consumption (non-, former, or current drinker), and physical activity (quartiles of total intentional exercise in MET min/week). Models were examined with adjustment for BMI and waist circumference simultaneously and with adjustment for each separately. Because associations of hormones with diabetes and IFG did not change after simultaneous adjustment and both BMI and waist circumference

Table 1—*Association of quartiles of sex hormones with normal fasting glucose, IFG, and type 2 diabetes status: Multi-Ethnic Study of Atherosclerosis (2000–2002)*

	IFG					Type 2 diabetes				
	Q1	Q2	Q3	Q4	P_{trend}*	Q1	Q2	Q3	Q4	P_{trend}*
Total testosterone (nmol/l)										
Mean (min–max)	8.90 (0.03–11.35)	12.81 (11.38–14.23)	15.87 (14.26–17.77)	22.05 (17.80–68.36)		8.90 (0.03–11.35)	12.81 (11.38–14.23)	15.87 (14.26–17.77)	22.05 (17.80–68.36)	
Non-Hispanic white	1.00	0.88 (0.61–1.27)	0.93 (0.64–1.34)	0.77 (0.53–1.11)	0.13	1.00	0.78 (0.46–1.29)	0.52 (0.29–0.94)	0.26 (0.13–0.54)	0.0005
Chinese	1.00	0.63 (0.33–1.19)	0.69 (0.37–1.31)	0.50 (0.25–0.97)	0.15	1.00	0.51 (0.22–1.21)	0.77 (0.34–1.74)	0.51 (0.21–1.27)	0.14
African American	1.00	1.07 (0.67–1.71)	1.15 (0.72–1.84)	0.85 (0.53–1.36)	0.73	1.00	0.75 (0.44–1.28)	0.78 (0.45–1.34)	0.77 (0.46–1.31)	0.64
Hispanic	1.00	0.76 (0.46–1.24)	0.88 (0.54–1.45)	0.68 (0.41–1.13)	0.43	1.00	0.72 (0.41–1.26)	0.77 (0.43–1.37)	0.40 (0.21–0.77)	0.009
All	1.00	0.86 (0.68–1.08)	0.93 (0.73–1.18)	0.73 (0.57–0.92)	0.06	1.00	0.72 (0.54–0.97)	0.70 (0.52–0.96)	0.49 (0.35–0.68)	0.0002
Bioavailable testosterone (nmol/l)										
Mean (min–max)	3.27 (0.02–4.20)	4.74 (4.23–5.21)	5.82 (5.24–6.46)	7.92 (6.49–53.44)		3.27 (0.02–4.20)	4.74 (4.23–5.21)	5.82 (5.24–6.46)	7.92 (6.49–53.44)	
Non-Hispanic white	1.00	0.86 (0.60–1.22)	0.90 (0.63–1.30)	0.95 (0.65–1.37)	0.57	1.00	0.63 (0.36–1.10)	0.67 (0.38–1.19)	0.71 (0.38–1.28)	0.12
Chinese	1.00	0.98 (0.51–1.89)	0.87 (0.47–1.61)	0.62 (0.32–1.20)	0.04	1.00	1.36 (0.59–3.15)	0.87 (0.37–2.04)	0.82 (0.33–2.06)	0.35
African American	1.00	1.45 (0.92–2.28)	1.33 (0.83–2.13)	1.00 (0.61–1.65)	0.97	1.00	1.10 (0.65–1.86)	1.03 (0.60–1.80)	1.29 (0.75–2.23)	0.21
Hispanic	1.00	0.81 (0.49–1.34)	1.00 (0.60–1.65)	0.63 (0.38–1.05)	0.22	1.00	0.93 (0.51–1.70)	1.19 (0.64–2.18)	1.03 (0.56–1.89)	0.94
All	1.00	0.98 (0.78–1.23)	1.01 (0.80–1.28)	0.83 (0.64–1.07)	0.16	1.00	0.91 (0.67–1.23)	0.92 (0.67–1.26)	0.98 (0.70–1.37)	0.65
SHBG (nmol/l)										
Mean (min–max)	25.3 (8.6–31.4)	36.1 (31.5–40.8)	46.4 (40.9–52.7)	70.1 (52.8–198.0)		25.3 (8.6–31.4)	36.1 (31.5–40.8)	46.4 (40.9–52.7)	70.1 (52.8–198.0)	
Non-Hispanic white	1.00	0.98 (0.68–1.40)	0.58 (0.40–0.85)	0.69 (0.48–1.01)	0.09	1.00	0.92 (0.52–1.61)	0.63 (0.35–1.12)	0.31 (0.16–0.60)	0.003
Chinese	1.00	1.13 (0.60–2.11)	0.66 (0.35–1.24)	0.90 (0.48–1.68)	0.84	1.00	0.79 (0.35–1.80)	0.42 (0.18–0.99)	0.48 (0.20–1.16)	0.15
African American	1.00	1.04 (0.65–1.67)	0.80 (0.50–1.29)	0.62 (0.38–1.00)	0.47	1.00	0.90 (0.53–1.55)	0.67 (0.39–1.16)	0.45 (0.26–0.80)	0.02
Hispanic	1.00	1.00 (0.62–1.62)	1.17 (0.72–1.90)	0.93 (0.57–1.54)	0.84	1.00	0.59 (0.34–1.01)	0.53 (0.30–0.93)	0.25 (0.13–0.48)	0.15
All	1.00	1.02 (0.81–1.29)	0.76 (0.60–0.97)	0.75 (0.58–0.97)	0.24	1.00	0.78 (0.58–1.05)	0.56 (0.41–0.76)	0.35 (0.24–0.49)	<0.0001
E2 (pmol/l)										
Mean (min–max)	67.4 (9.2–84.4)	99.4 (88.1–110.1)	125.4 (113.8–139.5)	178.2 (143.2–961.8)		67.4 (9.2–84.4)	99.4 (88.1–110.1)	125.4 (113.8–139.5)	178.2 (143.2–961.8)	
Non-Hispanic white	1.00	0.91 (0.63–1.30)	1.30 (0.91–1.86)	1.74 (1.19–2.53)	0.06	1.00	1.45 (0.78–2.69)	1.93 (1.05–3.57)	2.12 (1.10–4.07)	0.05
Chinese	1.00	1.63 (0.90–2.97)	1.93 (1.06–3.52)	1.70 (0.83–3.48)	0.08	1.00	1.47 (0.61–3.56)	1.78 (0.74–4.27)	3.29 (1.33–8.14)	0.006
African American	1.00	1.41 (0.82–2.40)	1.60 (0.95–2.72)	1.32 (0.79–2.19)	0.16	1.00	1.08 (0.58–2.01)	1.70 (0.95–3.04)	1.06 (0.59–1.90)	0.29
Hispanic	1.00	0.99 (0.61–1.62)	0.89 (0.55–1.47)	1.08 (0.65–1.78)	0.15	1.00	1.12 (0.62–2.03)	1.20 (0.67–2.16)	0.97 (0.52–1.82)	0.46
All	1.00	1.11 (0.88–1.40)	1.33 (1.06–1.69)	1.42 (1.11–1.81)	0.002	1.00	1.24 (0.88–1.68)	1.64 (1.19–2.24)	1.44 (1.03–2.01)	0.005
Dehydroepiandrosterone (nmol/l)										
Mean (min–max)	7.0 (0.9–9.1)	10.8 (9.2–12.5)	14.6 (12.5–17.1)	24.0 (17.1–149.6)		7.0 (0.9–9.1)	10.8 (9.2–12.5)	14.6 (12.5–17.1)	24.0 (17.1–149.6)	
Non-Hispanic white	1.00	1.03 (0.73–1.44)	0.98 (0.68–1.40)	1.22 (0.84–1.79)	0.02	1.00	0.69 (0.40–1.20)	0.82 (0.46–1.45)	0.79 (0.41–1.50)	0.75
Chinese	1.00	0.71 (0.34–1.49)	0.84 (0.41–1.72)	1.20 (0.59–2.46)	0.12	1.00	1.01 (0.38–2.67)	0.99 (0.38–2.58)	1.33 (0.50–3.53)	0.45
African American	1.00	1.41 (0.86–2.33)	1.82 (1.10–3.00)	1.57 (0.96–2.58)	0.19	1.00	1.68 (0.96–2.93)	1.84 (1.04–3.26)	1.41 (0.79–2.53)	0.22
Hispanic	1.00	1.14 (0.68–1.90)	1.18 (0.70–1.98)	1.37 (0.81–2.31)	0.03	1.00	0.64 (0.35–1.16)	0.90 (0.50–1.62)	0.84 (0.45–1.56)	0.67
All	1.00	1.07 (0.85–1.36)	1.16 (0.91–1.48)	1.32 (1.02–1.71)	0.0005	1.00	0.90 (0.67–1.22)	1.05 (0.76–1.43)	0.99 (0.70–1.40)	0.56

Data are OR (95% CI) unless otherwise indicated. ORs are adjusted for age, BMI, waist circumference, and in the pooled analysis, ethnicity. IFG: 100 mg/dl ≤ fasting glucose < 126 mg/dl; type 2 diabetes: fasting glucose ≥126 mg/dl or current use of diabetes medication. *P value from a model treating hormone as a continuous variable. Q, quartile.

were significant, results are presented with the simultaneous adjustment.

RESULTS — The prevalence of IFG and diabetes was 30 and 21% in African Americans, 32 and 9% in non-Hispanic whites, 35 and 20% in Hispanics, and 40 and 15% in Chinese, respectively.

Interactions between ethnicity and hormones for diabetes or IFG were not statistically significant when using quartiles of sex hormones ($P \geq 0.28$) or continuous hormone variables ($P \geq 0.19$). Because this may be a consequence of limited power, analyses are presented by ethnicity and also pooled (Table 1). For total testosterone, the ORs for the highest quartile compared with those for the lowest ranged from 0.26 to 0.77 for diabetes and from 0.50 to 0.85 for IFG. Similarly, all ORs for the highest quartile of sex hormone–binding globulin (SHBG) were <1.0 for diabetes and IFG. In contrast, ORs for estradiol (E2), especially in Chinese men, indicated positive associations with IFG and diabetes.

In the pooled analysis, the inverse associations of total testosterone and SHBG, and the positive association of E2, with type 2 diabetes were strong. SHBG was significantly but not linearly associated with IFG. Dehydroepiandrosterone was positively associated with IFG but not with diabetes. Adjustment for other confounders did not attenuate these associations (data not shown).

CONCLUSIONS — Despite adjustment for BMI and waist circumference, in analyses pooling ethnicities, we observed significant inverse associations of total testosterone and SHBG with diabetes and IFG, whereas E2 was positively associated. Our findings are consistent with the results of a large meta-analysis (1) that included 43 cross-sectional and prospective studies conducted from 1966 through 2005. The conclusions of the meta-analysis and the present findings differ from those of NHANES III (2), which was not included in the meta-analysis. NHANES III results showed associations for free and bioavailable testosterone but not for total testosterone, SHBG, or E2 with diabetes. The reasons for differences in results between our study and NHANES are unclear. The absence of associations for total testosterone and SHBG in NHANES III might be due to the younger age of its cohort (>20 years) compared with that in MESA (45–84 years), which would imply a shorter duration of diabetes and the relatively smaller number of cases of diabetes. Alternatively, the NHANES III study did not distinguish between type 1 and type 2 diabetes; in this younger population, a higher proportion of cases may have had type 1 diabetes.

Similar to results of other national surveys (http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm), our findings also demonstrated ethnic differences in prevalence of glucose disorders. Despite this, the tests for interactions suggest that associations of each hormone with prevalence of glucose disorders did not differ by ethnicity. Nevertheless, it is recognized that ethnic differences in physiological responses to sex hormones might occur and might be due to factors other than the serum hormone levels (5). Thus, it has been recommended that future studies should consider hormone metabolism, ligand interaction with receptor, receptor action, and enzyme and receptor gene polymorphisms (5).

This cross-sectional study could not examine the temporal nature of the association between testosterone and metabolic status, which is controversial. Arguments supporting each direction (6), as well as bidirectionality (7), have been offered. Some animal models suggest that diabetes in the rat causes a reduction in Leydig cell number and testosterone secretion (8,9), whereas others suggest that testosterone regulates insulin sensitivity and insulin gene expression (10,11). Recent intervention studies in humans have not resolved this issue (12,13,14).

In conclusion, our study provides additional evidence that sex hormones are associated with type 2 diabetes independently of BMI and waist circumference. Other prospective studies are needed to either replicate or refute our finding that the associations do not differ by ethnicity.

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