Endogenous Sex Hormones and the Development of Type 2 Diabetes in Older Men and Women: the Rancho Bernardo Study

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OBJECTIVE — To determine the prospective association between endogenous sex hormones and the development of type 2 diabetes in older men and women.

RESEARCH DESIGN AND METHODS — A standardized medical history was obtained, an oral glucose tolerance test was performed, and plasma samples for sex hormones and covariates were collected from ambulatory, community-dwelling men and women at baseline from 1984 to 1987. Approximately 8 years later (1992–1996), another medical history was obtained, an oral glucose tolerance test was performed, fasting and 2-h insulin levels were measured, and the homeostasis model assessment for insulin resistance (HOMA-IR) was evaluated. This report is based on the 294 men and 233 women, aged 55–89 years, who completed both visits and who did not have diabetes as determined by history or glucose tolerance test at baseline, as well as women who were postmenopausal and not taking replacement estrogen.

RESULTS — In age-adjusted correlation analyses, total testosterone was inversely and significantly related to subsequent levels of fasting and postchallenge glucose and insulin in men, whereas bioavailable testosterone and bioavailable estradiol were positively and significantly related to fasting and postchallenge glucose and insulin in women (all $P < 0.05$). There was similar significant association with insulin resistance (HOMA-IR) in unadjusted and multiply adjusted analyses ($P < 0.05$). There were 26 men and 17 women with new (incident) diabetes. The odds for new diabetes were 2.7 (95% CI 1.1–6.6) for men in the lowest quartile of total testosterone and 2.9 (1.1–8.4) for women in the highest quartile of bioavailable testosterone.

CONCLUSIONS — Low testosterone levels in men and high testosterone levels in women predict insulin resistance and incident type 2 diabetes in older adults.

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Both human (1–9) and animal studies (10,11) show differences by sex in the effects of endogenous sex hormones on insulin resistance. In men, low plasma testosterone is associated with obesity, upper body fat distribution, and increased levels of glucose and insulin (1–3), whereas hyperandrogenicity is associated with an increased risk for type 2 diabetes and cardiovascular disease in women (3–9). Most of these studies were cross-sectional.

Sex hormone–binding globulin (SHBG) is an indirect measure of androgenicity, because its concentration is mainly determined by free estrogen and testosterone (4,7–9,12,13). Several prospective studies show that low levels of testosterone and SHBG predict the development of type 2 diabetes in middle-aged (14,15) and elderly (16) men. One cross-sectional study shows that women with type 2 diabetes have high levels of free testosterone and low levels of SHBG (17). Low levels of SHBG alone did not significantly predict incident type 2 diabetes in middle-aged men (18); in contrast, low levels of SHBG alone predicted the development of type 2 diabetes in women (18,19). To our knowledge, there are no large prospective, population-based studies of total and bioavailable (non-SHBG bound) sex hormones as predictors of incident insulin resistance or type 2 diabetes in both men and women.

We previously reported a significant cross-sectional association between type 2 diabetes and lower total testosterone in men and higher bioavailable testosterone in women, measured by bioavailable (non-SHBG bound) sex hormones in Rancho Bernardo Study participants (20). The present study was designed to determine whether sex hormones predict future type 2 diabetes and whether the direction of the association is similar in men and women.

RESEARCH DESIGN AND METHODS

— Between 1984 and 1987, 82% of surviving residents (1,094 men and 1,385 women) of a southern California residential community participated in the Rancho Bernardo Heart and Chronic Disease Study (21). A total of 9 men and 295 women who were >55 years of age and had no diabetes were taking exogenous sex hormones. After excluding them, 687 men and 589 women were enrolled in the baseline study. During the next 8 years, 42% of men and 37% of women who participated in the baseline examination died before a follow-up

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Abbreviations: HOMA-IR, homeostasis model assessment for insulin resistance; OR, odds ratio; SHBG, sex hormone–binding globulin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Unadjusted baseline (1984–1987) characteristics among men and women according to diabetes status at follow-up (1992–1996) (Rancho Bernardo, CA)*

	Men		Women	
	Diabetes (n = 26)	No diabetes (n = 268)	Diabetes (n = 17)	No diabetes (n = 216)
Age (years)	68.3 ± 7.2	66.7 ± 7.7	72.3 ± 5.4	72.4 ± 6.2
BMI (kg/m^2)	26.5 ± 3.6	25.9 ± 3.0	24.5 ± 3.2	24.2 ± 3.4
Waist (cm)	94.0 ± 9.1	93.0 ± 8.3	79.7 ± 5.9	78.8 ± 8.9
Waist-to-hip ratio	0.91 ± 0.1	0.91 ± 0.1	0.81 ± 0.1	0.80 ± 0.1
Systolic blood pressure (mmHg)	143.6 ± 16.7*	132.5 ± 18.7	148.1 ± 16.9	140.9 ± 20.6
Diastolic blood pressure (mmHg)	80.4 ± 9.0	77.8 ± 8.3	78.9 ± 11.2	75.0 ± 9.3
Fasting glucose (mmol/l)	6.0 ± 0.5†	5.5 ± 0.6	5.7 ± 0.6*	5.3 ± 0.6
Postchallenge glucose (mmol/l)	8.3 ± 2.0†	6.4 ± 1.9	8.3 ± 1.6*	7.1 ± 1.7
Fasting insulin (pmol/l)	102.3 ± 73.9	79.4 ± 48.3	53.3 ± 26.6	65.9 ± 40.1
Postchallenge insulin (pmol/l)	820.4 ± 543.9†	440.0 ± 380.3	638.9 ± 273.6	571.5 ± 366.0
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.4 ± 0.4	1.6 ± 0.4	1.8 ± 0.4
Triglycerides (mmol/l)	1.6 ± 1.1	1.4 ± 0.8	1.3 ± 0.6	1.2 ± 0.6
HOMA-IR	4.5 ± 3.0	3.3 ± 2.0	2.2 ± 1.2	2.6 ± 1.6
Current smoking (%)	3.9	11.7	17.7	10.2
Daily alcohol (%)	66.7	80.2	69.2	69.8
Exercise ≥3 times/wk (%)	84.6	89.6	82.4	83.7

Data are means ± SD or %. *P < 0.01; †P < 0.001 versus no diabetes.

visit. Among survivors who were ambulatory and living locally, 74% (n = 294) of men and 62% (n = 233) of women participated in a follow-up visit (1992–1996); these individuals form the basis of this report.

A 75-g oral glucose tolerance test was performed in the morning after a 12-h fast. Fasting and postchallenge plasma glucose levels were measured by glucose oxidase assay. Fasting and postchallenge plasma insulin levels were determined by double-antibody radioimmunoassay (22).

Fasting insulin was used as a surrogate for insulin resistance. Fasting insulin levels were highly correlated with hyperinsulinemic euglycemic clamp results in persons without diabetes (23). Insulin resistance assessed by homeostasis model assessment for insulin resistance (HOMA-IR), a reliable marker for insulin resistance in large-scale epidemiological studies (24), was calculated as {fasting glucose (mmol/l) × fasting insulin (μU/ml)}/22.5 (25). HOMA-IR and fasting insulin were highly correlated in both sexes in the present study (r = 0.98, P < 0.0001).

Height, weight, waist girth, and hip girth were measured with subjects in light-weight clothing without shoes. BMI was calculated as weight (kg)/height (m)^2. Personal history of hypertension, diabetes, current cigarette smoking, daily alcohol consumption, regular exercise (≥3 times/week), and use of exogenous sex hormones were determined by standardized questionnaire and interview. Diagnosis of type 2 diabetes, impaired fasting glucose, and impaired glucose tolerance were based on World Health Organization criteria (26).

Informed consent was obtained from all subjects, and potential risks of the study were explained. The study was approved by the institutional review board of University of California, San Diego.

Between 1992 and 1993, hormones were measured in an endocrinology research laboratory by radioimmunoassay using first-thawed specimens from the 1984–1987 venipuncture. Bioavailable testosterone and bioavailable estradiol were determined using a modification of the ammonium-sulfate precipitation method of Tremblay and Dube (27). The sensitivity and intra- and interassay coefficients of variation for men and women were the same as previously reported (20). A total of 30 women in whom total estradiol levels were below the limit of detection were included in the analyses; undetectable hormone levels were assigned the smallest detectable level.

Data were analyzed using SAS version 8.1 statistical software (SAS Institute, Cary, NC). Because fasting and postchallenge insulin, HOMA-IR, and sex hormones (women) showed slightly skewed distributions, analyses were performed using log-transformed data. Although mean values are shown for untransformed data, all P values are based on log-transformed data.

Unadjusted associations between potential predictors and incident diabetes were evaluated using Student's t test and χ^2 test. Age-adjusted partial correlation coefficients were used to study associations between sex hormones and insulin resistance or type 2 diabetes. Multiple linear regression analyses were used to determine the independent association between sex hormones and insulin resistance. Persons with incident diabetes were excluded from this analysis because fasting insulin is a more valid marker for insulin resistance in persons without diabetes (23). Baseline age, BMI, systolic blood pressure, and HOMA-IR were evaluated as covariates, as well as smoking, alcohol, and exercise. Multiple logistic regression analyses were used to assess the independent contribution of sex hormones to incident type 2 diabetes. Baseline age, BMI, and systolic blood pressure were included in this model . For logistic regression models, sex hormones were analyzed as the lowest quartile (<8.6 nmol/l for total testosterone, <3.0 nmol/l for bioavailable testosterone, <58.7 pmol/l for total estradiol, <40.4 pmol/l for bioavailable estradiol) versus the top three quartiles in men, and highest quar-

Table 2—*Age-adjusted partial correlation coefficients between endogenous sex hormones at baseline and clinical measurements in older men (Rancho Bernardo, CA)*

	Testosterone	Bioavailable testosterone	Estradiol	Bioavailable estradiol
Baseline data (1984–1987)				
BMI	−0.248‡	−0.128*	0.001	0.057
Waist	−0.246‡	−0.121*	0.003	0.046
Waist-to-hip ratio	−0.156†	−0.064	−0.040	−0.018
Systolic blood pressure	−0.096	−0.076	0.078	0.067
Diastolic blood pressure	−0.037	−0.109	0.093	0.109
HDL cholesterol	0.284‡	0.022	0.104	−0.008
Triglycerides	−0.382‡	−0.074	−0.123*	0.018
Fasting glucose	−0.089	−0.006	−0.043	0.006
Postchallenge glucose	−0.159*	−0.049	0.019	0.057
Fasting insulin	−0.232‡	−0.084	−0.040	0.059
Postchallenge Insulin	−0.206†	−0.116	0.038	0.104
HOMA-IR	−0.238‡	−0.081	−0.044	0.059
Follow-up data (1992–1996)				
Fasting glucose	−0.174†	−0.013	−0.094	−0.047
Postchallenge glucose	−0.160*	0.016	−0.028	−0.043
Fasting insulin	−0.237‡	−0.067	−0.084	−0.035
Postchallenge insulin	−0.227‡	0.034	−0.101	0.007
HOMA-IR	−0.249‡	−0.064	−0.093	−0.039

Data are correlation coefficients. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

tile (≥0.7 nmol/l for total testosterone, ≥0.21 nmol/l for bioavailable testosterone, ≥25.7 pmol/l for total estradiol, and ≥14.7 pmol/l for bioavailable estradiol) versus the bottom three quartiles in women. All *P* values were two-tailed, and statistical significance was defined as $P < 0.05$.

RESULTS — Between baseline and follow-up, type 2 diabetes developed in 26 men (8.8%) and 17 women (7.3%). Mean (range) levels of total and bioavailable testosterone were 10.9 (0.63–20.2) and 3.7 nmol (0.05–7.2) in men, and 0.59 (0.04–3.23) and 0.16 nmol/l (0.01–0.96) in women; total and bioavailable estradiol were 74.7 (18.4–190.9) and 49.9 pmol/l (3.7–106.5) in men and 21.72 (7.3–135.8) and 11.1 pmol/l (0.7–51.4) in women.

Baseline fasting and postchallenge glucose were significantly higher in men ($P < 0.001$) and women ($P < 0.01$) with incident diabetes compared with persons without incident diabetes; postchallenge insulin was significantly higher in men with incident diabetes ($P < 0.001$). No differences were observed for age, BMI, waist girth, waist-to-hip ratio, fasting insulin, HDL cholesterol, triglycerides, HOMA-IR, smoking, alcohol, and exercise (Table 1).

Table 2 presents age-adjusted partial correlation coefficients for sex hormones with baseline and follow-up clinical data in men. Total and bioavailable testosterone were inversely correlated with baseline BMI and waist girth. Total testosterone was inversely associated with baseline waist-to-hip ratio and triglycerides, baseline and follow-up levels of fasting and postchallenge glucose and insulin, and HOMA-IR. Total testosterone was positively correlated with baseline HDL cholesterol.

In women, total and bioavailable estradiol were positively correlated with baseline BMI, waist girth, and triglyceride level. Bioavailable testosterone was positively correlated with baseline BMI, waist girth, diastolic blood pressure, and postchallenge insulin level. Total testosterone was positively correlated with baseline HDL cholesterol. Bioavailable estradiol and bioavailable testosterone were positively correlated with baseline fasting glucose and with follow-up fasting insulin and HOMA-IR (Table 3).

The association of baseline sex hormones and the development of insulin resistance assessed by follow-up HOMA-IR in persons without incident diabetes is shown in Table 4: model 1 adjusted for baseline age; model 2 adjusted for baseline age, BMI, systolic blood pressure, and HOMA-IR; and model 3 adjusted for these covariates in addition to smoking, alcohol, and exercise. In men, lower total testosterone levels predicted increased

Table 3—*Age-adjusted partial correlation coefficients between endogenous sex hormones at baseline and clinical measurements in older women (Rancho Bernardo, CA)*

	Testosterone	Bioavailable testosterone	Estradiol	Bioavailable estradiol
Baseline data (1984–1987)				
BMI	0.064	0.133*	0.133*	0.211†
Waist	−0.010	0.178†	0.195†	0.323‡
Waist-to-hip ratio	−0.040	0.114	−0.063	0.199†
Systolic blood pressure	0.096	0.131	0.095	0.064
Diastolic blood pressure	0.096	0.162*	0.015	0.064
HDL cholesterol	0.198†	0.079	−0.051	−0.099
Triglycerides	−0.126	0.028	0.137*	0.217†
Fasting glucose	−0.046	0.172*	0.038	0.163*
Postchallenge glucose	0.001	0.108	0.116	0.211†
Fasting insulin	−0.164	−0.155	−0.116	0.005
Postchallenge insulin	0.036	0.174*	0.040	0.166
HOMA-IR	−0.166	−0.135	−0.105	0.037
Follow-up data (1992–1996)				
Fasting glucose	−0.106	0.052	0.030	0.106
Postchallenge glucose	−0.001	0.104	0.067	0.148
Fasting insulin	−0.022	0.184*	0.016	0.150*
Postchallenge insulin	−0.075	0.105	0.104	0.115
HOMA-IR	−0.031	0.192*	0.021	0.160*

Data are correlation coefficients. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

Table 4—*Association of endogenous sex hormones with insulin resistance* in older men and women without incident diabetes by multiple linear regression analyses (Rancho Bernardo, CA)*

		Men		Women	
Independent variables†	Covariates†	β	*P*	β	*P*
Testosterone	Model 1	−0.37	0.001	−0.023	0.71
	Model 2	−0.24	0.02	0.020	0.76
	Model 3	−0.31	0.02	0.011	0.88
Bioavailable testosterone	Model 1	−0.10	0.39	0.15	0.003
	Model 2	−0.13	0.23	0.15	0.01
	Model 3	−0.15	0.28	0.15	0.02
Estradiol	Model 1	−0.13	0.24	0.035	0.61
	Model 2	−0.08	0.47	0.054	0.49
	Model 3	−0.05	0.64	0.025	0.77
Bioavailable estradiol	Model 1	−0.03	0.79	0.14	0.01
	Model 2	−0.07	0.49	0.15	0.02
	Model 3	−0.05	0.66	0.14	0.055

*Assessed by follow-up levels of HOMA-IR (1992–1996) as a dependent variable, results remained unchanged when using fasting insulin levels as a dependent variable; †independent variables and covariates at baseline (1984–1987). Model 1 includes baseline age; model 2 includes baseline age, BMI, systolic blood pressure, and HOMA-IR; and model 3 includes baseline age, BMI, systolic blood pressure, HOMA-IR, smoking, alcohol, and exercise.

levels of follow-up HOMA-IR ($P < 0.05$) in all models. In women, higher levels of bioavailable testosterone predicted increased levels of follow-up HOMA-IR ($P < 0.05$) in all models. Increased levels of bioavailable estradiol predicted increased levels of follow-up HOMA-IR after adjustment for baseline age, BMI, systolic blood pressure, and HOMA-IR ($P < 0.05$). After additional adjustment for lifestyle variables, bioavailable estradiol had a borderline significance ($P = 0.055$). When analyses were repeated with follow-up fasting insulin instead of HOMA-IR, results were unchanged in men and women (data not shown).

Multiple logistic regression analyses for predicting incident diabetes are shown in Fig. 1. After controlling for baseline age, BMI, and systolic blood pressure, low levels of total testosterone predicted incident diabetes in men (odds ratio [OR] 2.7, 95% CI 1.1–6.6, $P = 0.03$). In women, increased levels of bioavailable testosterone predicted incident diabetes after adjusting for baseline age, BMI, and systolic blood pressure (OR 2.9, 95% CI 1.1–8.4, $P = 0.04$). When we adjusted for waist circumference instead of BMI, the results were the same in men and women. Between baseline and follow-up, 2 men and 35 women began taking exogenous sex hormones. After excluding these persons, the results did not differ for either men or women (data not shown).

In men, incidence of diabetes was significantly higher in the lowest quartile for total testosterone than in the second and the third quartiles or than in all three of the higher quartiles combined (15.4 vs. 5.6 and 5.5 or 6.7%, $P < 0.05$); in women, incidence of diabetes was significantly higher in the highest quartile for bioavailable testosterone than in the second and the third quartiles or than in all three of the lower quartiles combined (14.6 vs. 3.5 and 3.7 or 5.0%, $P < 0.05$; data not shown).

CONCLUSIONS — In this prospective study, low levels of total testosterone in men and high levels of bioavailable testosterone in women predicted the development of type 2 diabetes. This finding is in agreement with our previous cross-sectional study, which found that men with impaired glucose tolerance had significantly lower levels of total testosterone, and women with impaired glucose

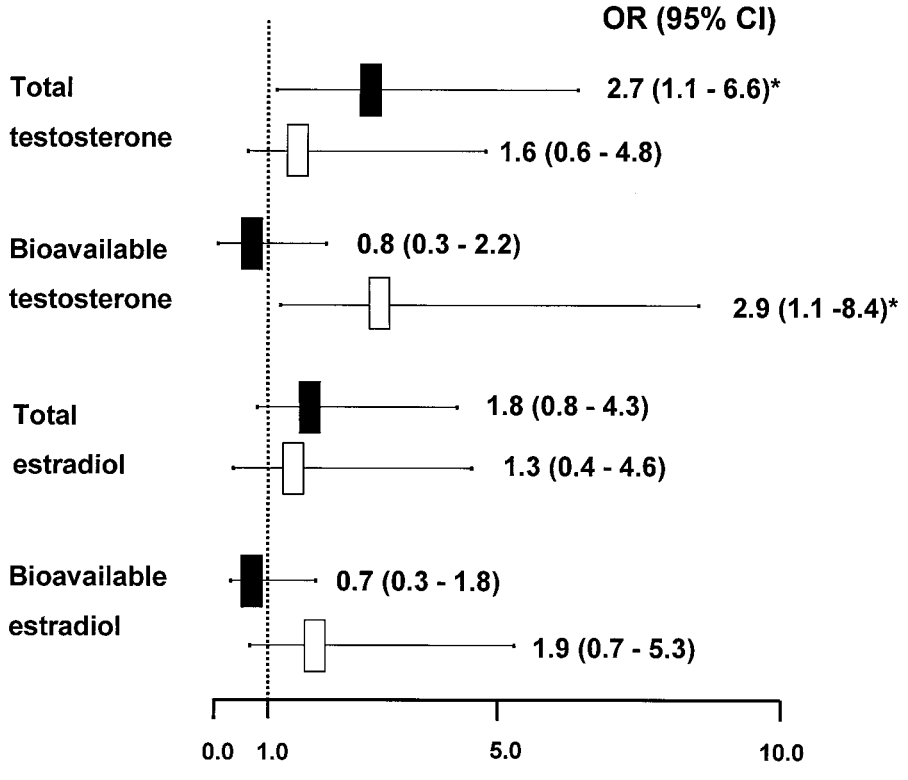

Figure 1—*Association of endogenous sex hormones with incident diabetes by multiple logistic regression adjusted for baseline age, BMI, and systolic blood pressure among older men (■) and women (□) without diabetes (Rancho Bernardo, CA). Sex hormone differences were analyzed as the lowest quartile versus the top three quartiles in men and the highest quartile versus the bottom three quartiles in women (*P < 0.05).*

tolerance or type 2 diabetes had significantly higher levels of bioavailable testosterone and total and bioavailable estradiol compared with those with normal glucose tolerance (20). Both studies were restricted to individuals >55 years of age who were not taking exogenous hormones. The present study excluded individuals with diabetes (by history or oral glucose tolerance test criteria) at baseline to evaluate incident (new) diabetes.

Hyperandrogenicity is associated with insulin resistance in women with polycystic ovary disease (28,29); it also decreases insulin sensitivity via an effect on the muscle glycogen synthase system in female rats (10,30). In men, the relation between testosterone and insulin sensitivity is more complicated. Castrated male rats showed increased insulin resistance, which was improved by low-dose testosterone replacement. However, treatment with high-dose testosterone worsened insulin resistance (11). This sexual dimorphism of testosterone on insulin resistance may be due to a plateau effect, in which variations in testosterone levels may contribute to insulin resistance in women whose androgenic activity is normally low but not in men who are already maximally androgenized. However, the biologic mechanism of the testosterone-insulin resistance association is uncertain.

Decline in both testicular and adrenal function with aging causes a decrease in androgen concentration in men (31). Testosterone levels are not much different before and after menopause in women (32).

A cross-sectional association between both hyperandrogenemia and hyperestrogenemia and type 2 diabetes was reported in postmenopausal women (33). The present study showed an association between higher levels of estrogen and subsequent development of insulin resistance in women. The main source of estrogen in postmenopausal women is aromatization of plasma androstenedione to estrone; estradiol is produced by interconversion of estrone and the aromatization of testosterone (34–36). Therefore, higher estrogen levels could result from the effects of higher androgen levels.

Total and bioavailable estradiol levels were relatively low in the present study, compared with other reports (17,37–39), possibly due to a more sensitive assay method (27). In addition, women had much lower values of estradiol compared with men. Older men have fourfold higher levels of estradiol than older women, due to higher testosterone and dehydroepiandrosterone levels for peripheral aromatization to estradiol (40).

The association between sex hormones and incident diabetes persisted after adjustment for baseline systolic blood pressure, although systolic blood pressure predicted incident type 2 diabetes in men (OR 1.3, 95% CI 1.1–1.6; data not shown). Hypertension is a major risk factor for type 2 diabetes (41), and isolated systolic hypertension was more strongly associated with abnormal glucose tolerance than diastolic hypertension in these older adults (42). No association was observed between BMI and incident diabetes in this older population of generally nonobese adults.

This study is limited by the use of a single hormone measurement. Testosterone, however, shows a high intraclass correlation, suggesting that a single measure reliably characterizes an individual (43). Although estradiol has wide intraindividual variation, such that a single assay characterizes an individual poorly (43,44), the present and previous studies (20) of this cohort found the expected associations between estradiol and measures of body fat, body fat distribution, and physical activity. Some investigators have remarked on the limited sensitivity of the estrogen assays, but only 13% of women (30 of 233) in this cohort had estradiol levels below the assay level of sensitivity, and exclusion of these women did not alter the results.

Nonresponse bias is common in studies of elderly persons. Approximately 42% of men and 37% of women who participated in the baseline examination died before the follow-up visit. Decedents were significantly older than persons who underwent both examinations, but their sex hormone levels did not differ significantly. Survivors who were eligible for follow-up and did not participate in the follow-up visit were also significantly older than respondents; again, their sex hormone levels did not differ significantly from those seen at the follow-up visit.

In conclusion, we observed differences by sex in the effects of endogenous sex hormones and deteriorating metabolic status. Low levels of total testosterone in older men and high levels of bioavailable testosterone in older women predicted the development of type 2 diabetes prospectively. In addition, low levels of total testosterone in men and high levels of bioavailable testosterone and estradiol in women were associated with the development of insulin resistance.

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