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Determinants of Serum Total and Free Testosterone Levels in Women over the Age of 65 Years

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Context: Little is known about testosterone (T) levels and their determinants in women of late postmenopausal age.

Objective: We describe levels of total and free T and selected factors that influence these levels in a random sample of older women.

Design: Levels of serum total T and free T by microdialysis were measured using ultrasensitive assays in 347 community-dwelling women aged 65–98 yr enrolled in the Cardiovascular Health Study. Cross-sectional analyses were performed to define factors associated with total and free T levels.

Results: In adjusted models: 1) total T levels declined with age until 80, whereas free T levels did not vary by age; 2) women with bilateral oophorectomy had 23% lower total T and 16% lower free T levels than those with at least one intact ovary; 3) oral estrogen users had total and free T levels that were 47% lower than never users; 4) obese women had 47% higher total T and 20% higher free T levels, and overweight women had 24% higher total T and 14% higher free T levels, than normal weight women; and 5) free T levels were 51% higher in black women. Corticosteroid users had 75% lower total T and 43% lower free T levels than nonusers.

Conclusions: Bilateral oophorectomy, estrogen use, corticosteroid use, and low body mass index are independent risk factors for lower T levels in women aged 65 yr and over. Although highly prevalent in women of this age, the physiological significance of low T levels in late postmenopausal women requires further investigation. **(*J Clin Endocrinol Metab* 92: 509–516, 2007)**

THE ROLE OF androgens in women is an area of mounting scientific and public interest. A female androgen insufficiency syndrome has been suggested, the effects of which include increased fatigue; diminished sense of well-being; and decreased libido, bone mass, muscle strength, and memory (1). Specific risk factors for lower testosterone (T) levels in younger women include bilateral oophorectomy, estrogen use, corticosteroid use, adrenal or pituitary disease, and HIV infection (2). However, few data are available regarding T levels in women over 65 yr old, despite continued production of androgens by the postmenopausal ovary in a gonadotropin-driven fashion, and whether the same determinants of T levels in younger women are relevant in later life (3, 4).

One explanation for the paucity of valid studies is the difficulty in assessing the very low T levels present in this population (5). Many published studies have used T assays with low sensitivity and poor reliability or included small numbers of women over 65 yr (6, 7). No prior studies have measured free T by dialysis in women over 65 yr. In 684 women aged 50–89 yr enrolled in the Rancho Bernardo Study, levels of total and bioavailable T were 40% lower in women with bilateral oophorectomy than in those with intact ovaries (8), a finding recently confirmed in another cross-sectional study with women up to age 75 yr (9). To our knowledge, no studies have examined the simultaneous impact of oophorectomy, estrogen use, and other relevant factors on T levels in late postmenopausal women. This information is essential if older women are affected by low androgen levels, for identification and avoidance of predisposing risk factors, and consideration of physiological testosterone replacement (10). Using highly sensitive assays, we aimed to describe levels of total T and free T by dialysis, selected factors that influence them, and the relationship between total and free T levels in late postmenopausal women. We hypothesized that the same factors that affect T levels in younger women would influence these levels in late postmenopausal women.

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Abbreviations: BMI, Body mass index; CHS, Cardiovascular Health Study; LC-MS/MS, liquid chromatography-tandem mass spectrometry; T, testosterone.

Subjects and Methods

Study population

The Cardiovascular Health Study (CHS) is a population-based, longitudinal study of risk factors for developing cardiovascular diseases in

5888 adults aged 65 yr and older (11). Enrollment of an original cohort of 5201 adults occurred between May 1989 and June 1990, and an additional cohort of 687 predominantly African-Americans enrolled in 1992–1993. Eligible individuals were identified from an age- and gender-stratified random sample of the Medicare eligibility rosters in four U.S. communities: Washington County, Maryland; Pittsburgh (Allegheny County), Pennsylvania; Sacramento County, California; and Forsyth County, North Carolina. To be eligible, individuals had to be noninstitutionalized, expecting to remain in the area for the following 3 yr, not under active cancer treatment, not wheelchair bound in the home, not requiring a proxy respondent at entry, and capable of providing consent. Household members of the sampled individual were recruited, if eligible. The institutional review boards of all four sites and the coordinating center at the University of Washington in Seattle approved the study, and all participants gave informed consent.

Random selection of the participants for our analyses was performed by the CHS coordinating center, using a computer program to generate a random list of identification numbers from all women with blood samples collected at the 1992–1993 visit. The first 350 identification numbers from that list were sent to the CHS Central Blood Analysis Laboratory for sample pulling; 348 had adequate sample for analysis and were included in our subcohort. The 1992–1993 visit included a detailed medical history, physical examination, and assessment of health status. Blood was drawn in the morning after a 12-h fast and serum was frozen in −70 C freezers for future investigations (12). Women in our subcohort were slightly older than in the CHS cohort but exhibited the same distribution of race, body mass index (BMI), estrogen use, and reproductive history.

Assessment of biochemical measures

Total T concentrations were measured by RIA using iodinated T as a tracer (13), which was validated against liquid chromatography-tandem mass spectrometry (LC-MS/MS), as described previously (14). These measurements demonstrated a correlation of 0.997 between the RIA and LC-MS/MS measurements (14). The sensitivity, defined as hormone concentration corresponding to 90% B/B_0 [percent bound in presence (B) and absence (B_0) of analyte] point, was 0.22 ng/dl (0.008 nmol/liter). The intra- and interassay coefficients of variation were 8.2 and 13.2%, respectively.

Free T concentrations were measured by a sensitive equilibrium dialysis assay (13), optimized to precisely and accurately measure low concentrations. The sensitivity of this assay is 0.6 pg/ml (2.0 pmol/liter); the intra- and interassay coefficients of variation were 4.2 and 12.3%, respectively.

The normative range for total and free T levels in different phases of the menstrual cycle, established in healthy, menstruating women, has been published using these assays (13).

Assessment of covariates

Sociodemographic characteristics included age, race, education, smoking status, alcohol use, age at menopause, prior hysterectomy, age at hysterectomy, prior oophorectomy, age at oophorectomy, and number of ovaries removed. BMI (kilograms per square meter), computed from objective measures, was categorized as less than 18.5, 18.5–24.9, 25–29.9, or 30 or greater. Medication use was determined from examination of medication bottles at the study visit.

Statistical analysis

Total and free T levels were summarized across subject characteristics using standard descriptive statistics. T levels were graphed against age; a lowess curve was applied to assess for a linear relationship. Log-transformed total *vs.* free T levels were plotted and Pearson's correlation coefficient was used to test for statistical significance. Paired *t* tests and one-way ANOVAs were performed to determine factors associated with the log-transformed total and free T levels. Factors found statistically significant at a $P < 0.1$ level, based on two-sided tests, were included in multivariable linear regression models. Estimates from these models were back transformed for interpretation on the original T scales, resulting in multiplicative rather than additive effects. For example, a variable with a backtransformed estimate of 2 for category X implies that a woman in category X has on average double the T levels of a woman in the reference category for that variable. Due to collinearity between race and educational status in our study population, only race was included in the final multivariate models.

Of 348 women in the original sample, one extreme outlier was excluded from the total T and four from the free T analyses. Two additional women were excluded from the free T analyses due to insufficient serum. Nine women taking oral corticosteroids were excluded from the regression models, due to their small number and extreme difference in values from the remainder of the sample.

Results

Demographic and reproductive characteristics

The 347 women ranged in age from 65 to 98 yr, with a mean age of 74 yr. Seventeen percent were black and 85% had at least a high school education (Table 1). The mean BMI in our study cohort was 26.8 kg/m^2. The majority (88%) had been pregnant at least once (Table 2). Overall, 43% of the women had undergone a hysterectomy and 16% reported bilateral oophorectomy. Sixty-three percent reported natural menopause, whereas 33% had undergone premenopausal hysterectomy; this information was unavailable in 4%. Nineteen percent were current oral estrogen users, and 27% had taken estrogen in the past. Nine women (3%) were taking oral corticosteroids.

Total and free testosterone levels

Serum total T levels ranged from 1 to 133 ng/dl (0.03 to 4.61 nmol/liter), with a mean of 20 ± 19 ng/dl (0.69 ± 0.66 nmol/liter) and a median of 15 ng/dl (0.52 nmol/liter). Serum free T levels ranged from 0.3 to 20.6 pg/ml (1.1 to 71.5 pmol/liter), with a mean of 2.8 ± 2.5 pg/ml (9.7 ± 8.7 pmol/liter) and a median of 2.0 pg/ml (6.9 pmol/liter). In a reference population of 34 healthy premenopausal women using the same assay (13), performed in the same laboratory, the range for total T was 11.5 to 77.8 ng/dl (0.40 to 2.70 nmol/liter), the mean peak (preovulation) total T was 44 ng/dl (1.53 nmol/liter) and the mean trough (early follicular) total T was 30 ng/dl (1.04 nmol/liter). The range for free T in these premenopausal women was 1.2 to 7.6 pg/ml (4.1 to 24.2 pmol/liter), the mean peak free T was 4.2 pg/ml (14.6 pmol/liter) and the mean trough free T was 3.2 pg/ml (11.1 pmol/liter).

Comparisons of total and free testosterone levels

Total and free T levels were highly correlated with each other ($r = 0.62$ for total *vs.* free testosterone, $P < 0.001$). The correlation between total and free T levels was poorest at the lowest levels of total and free T, as shown in Fig. 1. After removing the 60 women with total T levels 5 ng/dl or less, the correlation improved slightly, to 0.69 ($P < 0.001$).

Predictors of total and free testosterone levels: bivariate models

Total T levels appeared to have a nonlinear relationship with age, whereas there was no apparent relationship between free T and age (Fig. 2). In bivariate models, the lowest total T levels were found in subjects 75–79 yr old, whereas free T levels did not differ significantly by age group (Table 1). Otherwise, the predictors of total and free T levels were

TABLE 1. Total and free T levels within demographic categories

Variable	Sample (%)	Total T, mean ± SD (ng/dl) (n = 347)	Free T, mean ± SD (pg/ml) (n = 342)
Age (yr)			
65–69	15	22 ± 15[a]	2.7 ± 1.9
70–74	43	20 ± 20	2.8 ± 2.4
75–79	26	17 ± 18	3.1 ± 3.2
80+	16	23 ± 22	2.8 ± 2.1
Race			
White	83	19 ± 19[a]	2.6 ± 2.1[b]
Black	17	25 ± 20	4.2 ± 3.7
Education			
Less than high school	15	25 ± 23[a]	3.7 ± 3.6[a]
High school graduate	40	20 ± 17	2.8 ± 2.1
Some college	45	18 ± 18	2.6 ± 2.4
BMI (kg/m^2)			
<18.5	5	13 ± 13[b]	1.7 ± 0.5[a]
18.5–24.9	35	16 ± 19	2.4 ± 1.8
25–29.9	35	20 ± 17	2.9 ± 2.6
≥30.0	25	26 ± 22	3.4 ± 3.2
Smoking			
Never	49	21 ± 21	2.9 ± 2.5
Former	40	19 ± 19	2.7 ± 2.7
Current	11	20 ± 12	2.7 ± 2.2
Alcohol			
None	51	22 ± 20	3.1 ± 2.9
Less than seven times per week	40	18 ± 15	2.6 ± 2.0
7+ times per week	9	22 ± 30	2.4 ± 2.2

Multiply by 0.0347 to convert total T concentrations from nanograms per deciliter to nanomoles per liter. Multiply by 3.47 to convert free T concentrations from picograms per milliliter to picomoles per liter. *P* values are based on differences in mean values of log-transformed total and free T within the variable categories.

[a] $P < 0.05$.

[b] $P < 0.001$.

identical (Tables 1 and 2). White race, greater education, lower BMI, bilateral oophorectomy, present or past use of estrogens, and oral corticosteroid use were each individually associated with lower total and free T levels (Tables 1 and 2). Total and free T levels did not vary significantly by smoking status or alcohol intake.

Several reproductive variables were evaluated for potential influence on total and free T levels (Table 2). Total and free T levels were unrelated to prior pregnancy. The menopause type (natural *vs.* surgical) did not affect T levels, unless both ovaries were removed at the time of surgery. Total and free T levels were similar between women who underwent natural menopause and women who had a hysterectomy with ovaries left intact. Total and free T levels were significantly lower in women who had both ovaries removed, whether before or after their natural menopause, compared with women who never had ovaries removed, had one ovary removed, or who did not know their ovarian status.

Only nine women were taking oral corticosteroids in our study group. However, corticosteroid use had a greater effect on T levels than any of the assessed factors, with mean total T levels 75% lower than in noncorticosteroid users (Table 2). Because of the extreme differences in their T values, women who were taking oral corticosteroids were excluded from all multivariate analyses.

Predictors of total and free testosterone levels: multivariate models

In models including age, race, BMI, number of ovaries removed, and estrogen use, age was a predictor of total T levels. Women over age 70 yr had lower total T levels than those 65–69 yr (Table 3). Race was not a statistically significant determinant of total T levels after adjusting for the other covariates. Total T levels were linearly associated with BMI ($P = 0.005$). Obese women (BMI ≥ 30 kg/m^2) had 47% higher total T levels ($P = 0.003$) and overweight women (BMI 25–29.9 kg/m^2) 24% higher total T levels ($P = 0.07$) than women with a BMI between 19 and 25 kg/m^2. Women taking oral estrogens at the time of the study visit had total T levels 47% lower than those who had never taken estrogen ($P < 0.001$). Participants who were past users had intermediate levels between current and never users, with levels 16% lower than those who had never taken estrogen, although this was not statistically significant. Women with bilateral oophorectomy had 23% lower total T levels than those with at least one intact ovary ($P = 0.05$).

In multivariate models, age was not a predictor of free T levels, with similar estimates across all age groups (Table 4). Black women had 51% higher free T levels than white women ($P < 0.0001$). Free T levels were linearly associated with BMI. Obese women (BMI ≥ 30 kg/m^2) had 20% higher free T levels ($P = 0.05$) and overweight women (BMI 25–29.9 kg/m^2) had 14% higher free T levels ($P = 0.11$) than women with a BMI between 19 and 25 kg/m^2. Current and past estrogen use were each associated with lower free T levels, with 47% lower levels in current users ($P = 0.01$) and 22% lower in past users ($P = 0.03$). Women with bilateral oophorectomy had 16% lower free T levels than women with at least one intact ovary ($P = 0.06$). In models replacing age with years since meno-

TABLE 2. Total and free T levels by reproductive variables and medications

Variable	Sample %	Total T, mean ± SD (ng/dl) (n = 347)	Free T, mean ± SD (pg/ml) (n = 342)
Pregnancies			
None	12	19 ± 19	2.4 ± 1.9
At least one	88	20 ± 19	2.9 ± 2.6
Years since menopause			
≤20	18	18 ± 19	2.4 ± 1.7
21–25	28	19 ± 16	2.8 ± 2.7
26–30	23	22 ± 21	3.3 ± 2.9
31–35	13	24 ± 25	3.2 ± 3.2
36+	18	18 ± 15	2.7 ± 2.2
Hysterectomy			
Unknown	4	23 ± 28	2.6 ± 1.6
No	53	20 ± 20	2.9 ± 2.7
Yes	43	20 ± 18	2.8 ± 2.4
Type of menopause			
Unknown	4	25 ± 30	2.6 ± 1.6
Natural	63	20 ± 19	2.9 ± 2.6
Surgical	33	20 ± 18	2.8 ± 2.5
No. of ovaries removed			
Unknown	13	24 ± 24[a]	3.3 ± 3.6[b]
0	63	20 ± 19	2.8 ± 2.1
1	8	24 ± 21	3.5 ± 3.7
2	16	13 ± 12	2.4 ± 2.4
Estrogen use			
Never	54	23 ± 20[c]	3.2 ± 2.7[c]
Past	27	17 ± 16	2.4 ± 1.7
Current	19	14 ± 18	2.5 ± 2.9
Oral corticosteroid use			
No	97	20 ± 19[c]	2.8 ± 2.4[a]
Yes	3	5 ± 5	1.6 ± 1.3

Multiply by 0.0347 to convert total T concentrations from nanograms per deciliter to nanomoles per liter. Multiply by 3.47 to convert free T concentrations from picograms per milliliter to picomoles per liter. *P* values are based on differences in mean values of log-transformed total and free T within the variable categories.

[a] $P < 0.01$.

[b] $P < 0.05$.

[c] $P < 0.001$.

pause, there was no significant association between calculated number of years since menopause and total or free T levels.

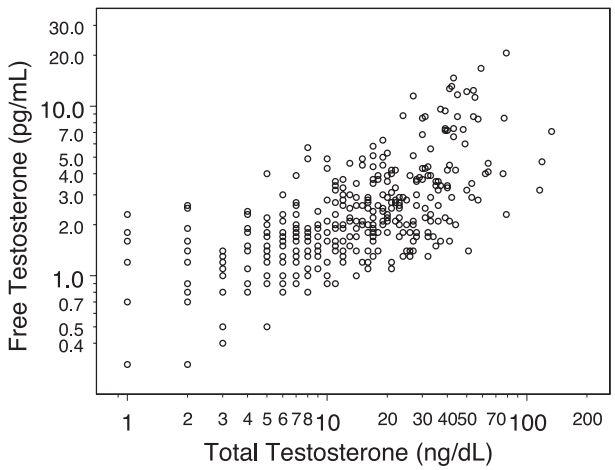

FIG. 1. Total T (nanograms per deciliter) *vs.* free T (picograms per milliliter).

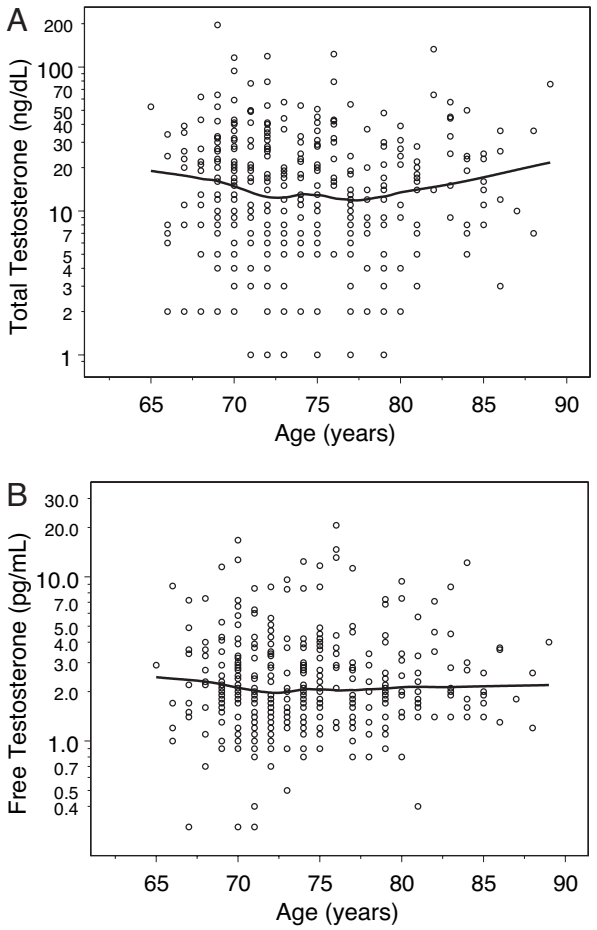

FIG. 2. A, Total T (nanograms per deciliter) *vs.* age. B, Free T (picograms per milliliter) *vs.* age.

Combined effect of ovarian removal and estrogen use

There was no evidence of synergy between the effects of ovarian removal and estrogen use (*P* value for interaction term = 0.43). Indeed, once both ovaries had been removed or estrogen was taken, the other risk factor had no additional impact on total or free T levels.

Discussion

Our data, obtained from women in late postmenopause heterogeneous in age, race, reproductive history, and estrogen replacement, suggest that a distribution shift occurs in T levels with advanced age. Although the mean total T levels in our study population are half and the free T levels two thirds of those seen in premenopausal women (13), the same factors that affect the production of T in premenopausal women also are influential in elderly women whose time of menopause averaged 25 yr earlier.

Unlike dehydroepiandrosterone sulfate or IGF-I, which demonstrate progressive declines with age (15–17), total and free T levels did not decrease linearly in these elderly women, even after adjusting for other confounders of the age-T relationship. The adjusted models of total T suggest a decrease with age until 80 yr, followed by a slight increase in levels. Whether the higher T levels seen in the

TABLE 3. Independent determinants of total T levels

Variable	Effect of determinant[a]	95% CI	*P* value	Higher/lower than reference group, %
Age (yr)			0.03	
65–69	1.00			Reference
70–74	0.74	0.55, 0.98	0.04	26% lower
75–79	0.65	0.47, 0.90	0.01	35% lower
80+	0.90	0.63, 1.28	0.54	10% lower
Race			0.19	
White	1.00			Reference
Black	1.20	0.92, 1.57	0.19	20% higher
BMI (kg/m^2)			0.005	
<18.5	0.72	0.45, 1.16	0.17	28% lower
18.5–24.9	1.00			Reference
25–29.9	1.24	0.98, 1.56	0.07	24% higher
≥30.0	1.47	1.14, 1.89	0.003	47% higher
Ovaries removed			0.05	
0, 1, or unknown	1.00			Reference
2 removed	0.77	0.59, 1.00	0.05	23% lower
Estrogen use			<0.0001	
Never	1.00			Reference
Past	0.85	0.67, 1.06	0.15	15% lower
Current	0.53	0.41, 0.70	<0.0001	47% lower

R^2 = 0.166645. CI, Confidence interval.

[a] Analysis based on log-transformed data for total T. Values are multiplicative effects on total T, generated from antilogs of adjusted effects, reported as a fold effect, compared with reference group. Estimates are reported from a multivariate model that included age, race, BMI, ovarian status, and estrogen use.

oldest women are a result of survival bias or a true physiological phenomenon cannot be determined in this cross-sectional analysis. Free T levels did not differ by age in our study. Other studies have not measured free T by dialysis in women 65 yr or older but have shown either a U shape or decline with age using other measures (8, 9). When we replaced age with time since menopause, we saw no relationship between this alternate time axis and total or free T levels, consistent with findings from other studies suggesting no impact of menopause on T production (8, 9, 18).

The factor with the greatest impact on T levels in these older women was corticosteroid use. Exogenous corticosteroids have been shown in small studies of premenopausal (19, 20) and postmenopausal (21) women to lower T levels by decreasing both adrenal androgen production and ovarian steroidogenesis through multiple inhibitory effects on the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-ovarian axes (22). Therefore, it is not surprising that free and total T levels were low in this group. Our findings also suggest that if T is biologically

TABLE 4. Independent determinants of free T levels

Variable	Effect of Determinant[a]	95% CI	*P* value	Higher/lower than reference group, %
Age (yr)			0.64	
65–69	1.00			Reference
70–74	0.93	0.76, 1.14	0.50	7% lower
75–79	1.03	0.82, 1.29	0.83	3% higher
80+	1.02	0.80, 1.32	0.86	2% higher
Race			<0.0001	
White	1.00			Reference
Black	1.51	1.25, 1.83	<0.0001	51% higher
BMI (kg/m^2)			0.11	
<18.5	0.86	0.59, 1.24	0.41	14% lower
18.5–24.9	1.00			Reference
25–29.9	1.14	0.97, 1.34	0.11	14% higher
≥30.0	1.20	1.00, 1.44	0.05	20% higher
Ovaries removed			0.06	
0, 1, or unknown	1.00			Reference
2 removed	0.84	0.69, 1.01	0.06	16% lower
Estrogen use			0.02	
Never	1.00			Reference
Past	0.78	0.71, 0.98	0.03	22% lower
Current	0.53	0.65, 0.95	0.01	47% lower

R^2 = 0.138638. CI, Confidence interval.

[a] Analysis based on log-transformed data for free T. Values are multiplicative effects on free T, generated from antilogs of adjusted effects, reported as a fold effect, compared with reference group. Estimates are reported from a multivariate model that included age, race, BMI, ovarian status, and estrogen use.

relevant in older women, this would be the group that would experience the most adverse consequences due to their very low levels.

Women with both ovaries removed were also found to have lower total and free T levels. This effect was specific to the ovaries; there was no impact of hysterectomy on T levels unless both ovaries were removed at the time of surgery. Our finding is consistent with a study in which T levels were determined before and after oophorectomy in 16 postmenopausal women, with a 50% decline after oophorectomy (23) and two other cross-sectional studies examining this risk factor in late postmenopausal women (8, 9).

Current estrogen use had a similar impact on total and free T levels in our study, suggesting that SHBG elevation did not entirely explain the estrogen effect. Our results may reflect an additional estrogen effect on ovarian T production via negative feedback on LH production. Our findings concur with studies of early postmenopausal women in which total and calculated free T decreased with estrogen use (24, 25) but differ from studies in which only the calculated free T declined (26, 27). Our data also imply a mild effect of past estrogen use on T levels, although other unmeasured factors may account for this observation. Whether a protracted effect on T production occurs from prior estrogen use requires validation in other studies. We were unable to demonstrate synergy or even an additive effect, between ovarian removal and estrogen. For example, once a woman had undergone bilateral oophorectomy, no additional effect of estrogen use could be detected.

Race was a strong predictor of free but not total T levels, even after adjusting for other confounding factors, including BMI, suggesting differences in T binding between black and white women. In more than 2000 perimenopausal women enrolled in the Study of Women's Health Across the Nation (SWAN), total T and SHBG levels did not differ between African-American and Caucasian women (28). We are unaware of data suggesting a mechanism for this finding, which could also be attributable to unmeasured confounders.

Our data show a linear relationship between T levels and BMI that is stronger for total than free T. Other studies have shown associations between T and BMI, insulin resistance, and the metabolic syndrome in peri- or postmenopausal women (8, 18, 28–32). This association suggests a relationship between T and insulin resistance in postmenopausal women that is either a generalized phenomenon or suggestive of polycystic ovary syndrome physiology many years after menopause. The direct relationship between BMI and T levels in women contrasts strikingly with that in men, in which BMI is inversely correlated with total T levels (33).

There is considerable controversy surrounding the measurement of T levels, particularly in women, and any assay has the potential for artifact at the lowest levels (5). Our total T levels were measured with a high-sensitivity assay optimized in the female range and validated against mass spectrometry methods (LC-MS/MS) (14). Our free T levels were measured via equilibrium dialysis, considered the gold standard for free T measurement (5, 34). Because of the precision of our assays, we were able to detect the impact of different factors that affect T levels in postmenopausal women, even at the very low T levels present in our aged study population. In our study, the major predictors of total and free T levels, except race, were the same as in younger women. However, the magnitudes of the effects of these predictors differed for total and free T. Whether sufficient additional information is obtained from the technically challenging equilibrium dialysis assay, compared with use of total T or free T calculations using SHBG, to merit its use clinically in late postmenopausal women remains to be determined. Continued research on the clinical implications of lower *vs.* higher total and free T levels in older women is needed to answer this question.

The strengths of our study include its population-based sample, which was not selected based on symptoms or reproductive characteristics that could be related to T levels; the richness of data collected on various reproductive and health characteristics; and the use of highly sensitive assays. However, several limitations should be acknowledged. First, there is the potential for misclassification of predictor variables, especially menopause age, oophorectomy history, and prior estrogen use due to imprecise recall of events occurring many years previously. In the Rancho Bernardo Study, hysterectomy and oophorectomy status was validated by operative records in a subgroup of 228 women. They found that 96% of women who reported bilateral oophorectomy were correct, whereas 33% of women reporting ovarian conservation had bilateral oophorectomy (8). This suggests that our estimates for T level reductions after oophorectomy likely underestimate the true impact of hysterectomy. Second, our analysis is cross-sectional in nature; thus, we are unable to assess the effects of time or reproductive variables in the same woman over time. Third, although we determined several significant predictors of T levels in older women, the value of r^2 was less than 17% for all adjusted models. This suggests that there were multiple unknown determinants of T levels in this age group, including genetic factors, unaccounted for in our models.

The clinical relevance of a specific T level is unknown. For example, lower sexual function is unassociated with lower T levels in women (35). The levels we observed are lower than those seen in premenopausal women but higher than those seen in women with pituitary disease (36) and HIV (13, 37, 38). According to the Princeton Consensus Panel on Female Androgen Deficiency Syndrome, a working definition of female androgen insufficiency, to be used in conjunction with symptoms, is the bottom quartile of the normal range for free T for 20- to 40-yr-old women (1). Using this laboratory cutoff and the data available for our assay, 62% of the women in our study would meet this criterion. As in men, any definition of androgen insufficiency should be associated with other clinical signs or symptoms that are improved with T therapy (39). However, if low T levels have an effect on physiological parameters in women, then the risk-benefit ratio of bilateral oophorectomy at the time of hysterectomy should be reevaluated. Furthermore, the detrimental effects of estrogen therapy in late postmenopausal women, as demonstrated in the Women's Health Initiative (40), may not be attributable entirely to the direct effects of estrogen but also partially due to their effects in lowering T. Because estrogen administration lowers T levels, using an estrogen-alone comparison group in estrogen-testosterone studies in postmenopausal women with intact ovaries does not allow exclusive evalu-

ation of T therapy. Additional research is required to clarify the role of T in women of all ages.

There is growing evidence of improvement in some domains of sexual function in response to T therapy in women who have had oophorectomy (41–43), but data are lacking on the effects of T supplementation in late postmenopausal women on these and other outcomes, including muscle, bone, and cognition (10). T therapy use in women of this age group is untested and requires clarification of the risk to benefit ratio, target population, and desirable T level before such studies are conducted (10, 44, 45).

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