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Androgen Levels in Adult Females: Changes with Age, Menopause, and Oophorectomy

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Context: Changes in androgen levels across the adult female life span and the effects of natural menopause and oophorectomy have not been clearly established.

Objective: The objective of this study was to document the effects of age on androgen levels in healthy women and to explore the effects of natural and surgical menopause.

Design, Setting, and Participants: A cross-sectional study was conducted of 1423 non-healthcare-seeking women, aged 18–75 yr, randomly recruited from the community over 15 months.

Main Outcome Measures: Serum levels by age of total testosterone (T), calculated free T, dehydroepiandrosterone sulfate, and androstenedione in a reference group of women free of confounding factors. Women in the reference group had no usage of exogenous steroid therapy; no history of tubal ligation, hysterectomy, or bilateral oophorectomy; and no hyperprolactinemia or polycystic ovarian syndrome. The effects of natural and surgical menopause on sex steroid levels were also examined.

Results: In the reference population (n = 595), total T, calculated free T, dehydroepiandrosterone sulfate, and androstenedione declined steeply with age ($P < 0.001$), with the decline of each being greater in the earlier than the later decades. Examination of serum androgen levels by year in women aged 45–54 yr showed no independent effect of menopausal status on androgen levels. In women aged 55 yr or older, those who reported bilateral oophorectomy and were not on exogenous steroids had significantly lower total T and free T levels than women 55 yr or older in the reference group.

Conclusions: We report that serum androgen levels decline steeply in the early reproductive years and do not vary because a consequence of natural menopause and that the postmenopausal ovary appears to be an ongoing site of testosterone production. These significant variations in androgens with age must be taken into account when normal ranges are reported and in studies of the role of androgens in women. **(*J Clin Endocrinol Metab* 90: 3847–3853, 2005)**

KNOWLEDGE OF THE physiological roles of androgens in women is limited. A major factor contributing to this knowledge gap is the uncertainty of what is normal in terms of serum androgen levels in women of differing ages. Studies to date addressing this have been limited by the inclusion of small numbers of women of limited age ranges (1, 2), and/or by reproductive status (3, 4), insensitivity of most assays of total and free testosterone (T) at the lower end of the reproductive female range (5), and failure in some studies to take into account the diurnal and cyclical variations in androgen levels for blood sampling.

There is growing interest in the role for androgen therapy for women, specifically T and the adrenal preandrogen dehydroepiandrosterone (DHEA). DHEA is sold over the counter in the United States, and inclusion of T in postmenopausal hormone therapy regimens is becoming more widespread. T preparations specifically for use in women are now undergoing phase 3 clinical trials, hence the need for age-specific validated normal ranges of the most commonly measured androgens in women as an initial basis for exploring the consequences of a woman having levels outside the age-specific range.

We have measured serum androgen levels in a large community-based group of women aged from the early reproductive years to many years post menopause to describe normative ranges by decade for total T, calculated free T, DHEA-sulfate (DHEAS) and androstenedione. To study normal physiology, we report androgen levels by decade in a reference group of women who were free of factors known to modify androgen levels. We have also explored the effects of natural and surgical menopause on the levels of these androgens.

Subjects and Methods

Study population

Participants were women aged 18–75 yr, recruited from April 2002 until August 2003 from Australia's southeastern state of Victoria, which according to the 2001 census, had a female population of approximately 1.9 million over the age of 15 yr. A database of eligible women was created using the following methodology: women were recruited by telephone using a database of individuals from household addresses selected at random on a weekly basis from Australian electoral areas. In Australia, because voting is compulsory, every adult must be registered on the electoral roll. Each electoral area was divided into sampling points of approximately equal numbers of 25,000 each. Melbourne had 105 sampling points, and country Victoria had 43 sampling points. Starting addresses were selected at random from the electoral roll for each of the sampling points. Interviews were conducted in person on Saturdays and Sundays between 0900 and 1600 h. Eight interviews were conducted per

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Abbreviations: BMI, Body mass index; CV, coefficient(s) of variation; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; PCOS, polycystic ovary syndrome; T, testosterone.

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sampling point. Only one eligible person was recruited per household, and people recruited to the sample tend to stay on the active database for about 2 yr. For this study, the database as of May 2002 was used initially, with eventual inclusion of past members of the database, back to 1998, to recruit sufficient women to the study.

Women from the database underwent telephone screening. Women were excluded if they were pregnant or less than 6 wk postpartum or had experienced any of the following in the preceding 3 months: an acute psychiatric illness; acute renal, liver, cardiovascular disease or any other acute major illness; gynecological surgery; or active malignancy or cancer treatment, excluding nonmelanotic skin cancer.

Eligible participants were asked to attend for a single morning fasting blood test and measurement of height (centimeters), weight (kilograms), and waist and hip circumference (centimeters). Premenopausal women attended after d 8 in the cycle to avoid the early follicular phase nadir of testosterone production. The women completed a personal profile questionnaire consisting of questions about general demographic details, menstrual pattern, acne, hirsutism, past gynecological surgery, current medical and psychiatric treatment, exercise, and alcohol and tobacco use.

The study protocol was approved by the Human Research and Ethics Committee, Southern Health, Clayton, Australia, and all participants provided written informed consent.

Sample size. This work is part of a study of the relationship of androgens and sexual function. The original sample size was related to the primary hypothesis for that study. The findings from this aspect of the study will be reported separately.

Definition of the reference group

We defined the reference group of women from within the study population to establish normative androgen values by decade. Subjects were excluded from the reference group if any of the following applied: use of exogenous steroid therapy (estrogen- and/or progestin-containing contraceptive agents of any delivery method, postmenopausal hormone therapy including topical or vaginal preparations, androgens, antiandrogens, or glucocorticoid or mineralocorticoid agents), bilateral oophorectomy, hysterectomy, tubal ligation, hyperprolactinemia (prolactin $>$ 550 mIU/liter; normal range, 50–500 mIU/liter), or polycystic ovarian syndrome (PCOS). PCOS was defined by a woman having at least two clinical features of this condition: self-reported menstrual irregularity or hirsutism; LH-to-FSH ratio greater or equal to 2:1; SHBG less than 30 nmol/liter (normal range, 27–109 nmol/liter), and free androgen index (total T/SHBG $\times$ 100) greater than 4.5% (normal range, 1.0–4.5%).

Effect of bilateral oophorectomy on androgen levels

We compared serum androgen levels of women who reported a bilateral oophorectomy and were otherwise comparable with women in the reference group (normoprolactinemia, and not taking exogenous systemic steroids of any form) with values determined for the women in the reference group.

Definition of menopause

Menopausal status was based on the responses to the personal profile questionnaire about cessation of menses or time of vasomotor symptom onset in the case of hysterectomy. Because determination of menopausal status was not clear-cut in some instances, we used a decision tree for classification. In consecutive order, we looked at whether women were aged less than 55 or 55 yr and older, stated an age at menopause, had regular menses or not, and whether they were on the oral contraceptive pill or hormone therapy. Finally, we looked at FSH and estradiol levels to decide the menopausal classification

Laboratory procedures

Fasting serum samples were stored at −80 C until assayed. Analysis of serum for all hormones was performed in the Clinical Biochemistry Department of Mayne Health Dorevitch Pathology Laboratory, Melbourne, Victoria, Australia.

Total T was measured by a direct manual RIA method (Biosource Europe S.A., Nivelles, Belgium) using antibody-coated tubes and iodine-labeled T tracer (500 μl). Mean between-batch coefficients of variation (CV) were 12.8, 9.7, 8.8, and 7.1% at 0.17, 0.61, 1.77, and 11.5 nmol/liter (n = 100), respectively; mean within-batch CV were 10.5, 5.3, 4.2, and 4.7% at the same concentrations (n = 20). This methodology was validated against a widely published conventional RIA that included organic solvent (ethylacetate:hexane, 3:2) extraction and Celite column partition chromatography before RIA (6) in 259 of the study samples. The direct manual RIA for testosterone used in this study has also previously been validated against the process of equilibrium dialysis in men and postmenopausal women (7). Samples with T values less than 0.2 nmol/liter were reported as less than 0.2 nmol/liter, but for statistical analysis we assigned these a value of 0.1. Free T was calculated using the Sodergard equation (8). SHBG and DHEAS were measured by a solid-phase, two-site chemiluminescent enzyme immunometric assay using the Immulite automated analyzer (Diagnostic Products Corp., Los Angeles, CA). The intra- and interassay CV for SHBG are 6.5 and 8.7%, respectively; the detection limit is 0.2 nmol/liter. For DHEAS, the intraassay CV is 6.8–9.5%, and interassay CV is 9.2–12.7%. Androstenedione was measured by direct RIA (DSL Inc., Webster, TX). Interassay CV is 5.8–10.4%.

Statistical analysis

Serum levels of total T, calculated free T, DHEAS, and androstenedione were reported for the reference group by decade as mean (SD), median, minimum, maximum, and 10th and 90th percentiles. For the descriptive analysis, participants were divided into six age groups: 18–24, 25–34, 35–44, 45–54, 55–64, and 65–75 yr. The first three groups therefore consisted of women who were mostly premenopausal, the final two groups represented women in the postmenopausal state, and the group aged 45–54 yr included both pre- and postmenopausal women. The youngest age group represents an incomplete decade because recruitment was limited to women 18 yr and above. The relationships between androgens and age are presented graphically as scatter plots and box and whisker plots and, in the case of SHBG, a fitted Lowess curve (a means of fitting a smooth nonparametric regression curve to a scatter plot).

Linear regression was used to model independent determinants of serum levels of androgens, including age measured in years and menopausal status. We also explored the effect of menopause on androgen levels by presenting androgen levels per individual year for women in the age group 45–54 yr, in which decade there were sufficient numbers of both pre- and postmenopausal women for comparison. The effect of oophorectomy on androgens was assessed using the *t* test for independent means; this was reported in women older than 55 yr to limit the confounding effect of age and because the older age groups included sufficient numbers of women who had undergone oophorectomy. All reported *P* values are two sided with significance defined as $P < 0.05$. Analyses were performed with SPSS statistical software (version 11.5; SPSS Australasia Pty. Ltd., North Sydney, Australia) or STATA statistical software (version 8.0, Stata Corp, College Station, TX).

Results

A total of 1423 women completed the study (Fig. 1). Of these, 80% were Australian born, and fewer than 2% of the whole group were non-Caucasian. A total of 595 women fulfilled the criteria for the reference group (Table 1). The mean age (SD) of the reference group was 48.5 (14.2) yr, and their mean body mass index (BMI) (SD) was 27.4 (6.9) kg/m^2. For weight, BMI, smoking, and parity the reference group reflected the total study population from which they were drawn. However, because of the difficulty recruiting younger women to the study and the prevalence of use of the oral contraceptive pill among young women, there were only 22 women less than 25 yr old who were eligible for the reference group.

All androgens show a decline with age (Tables 2 and 3 and Fig. 2). The decline with age is such that the mean total T

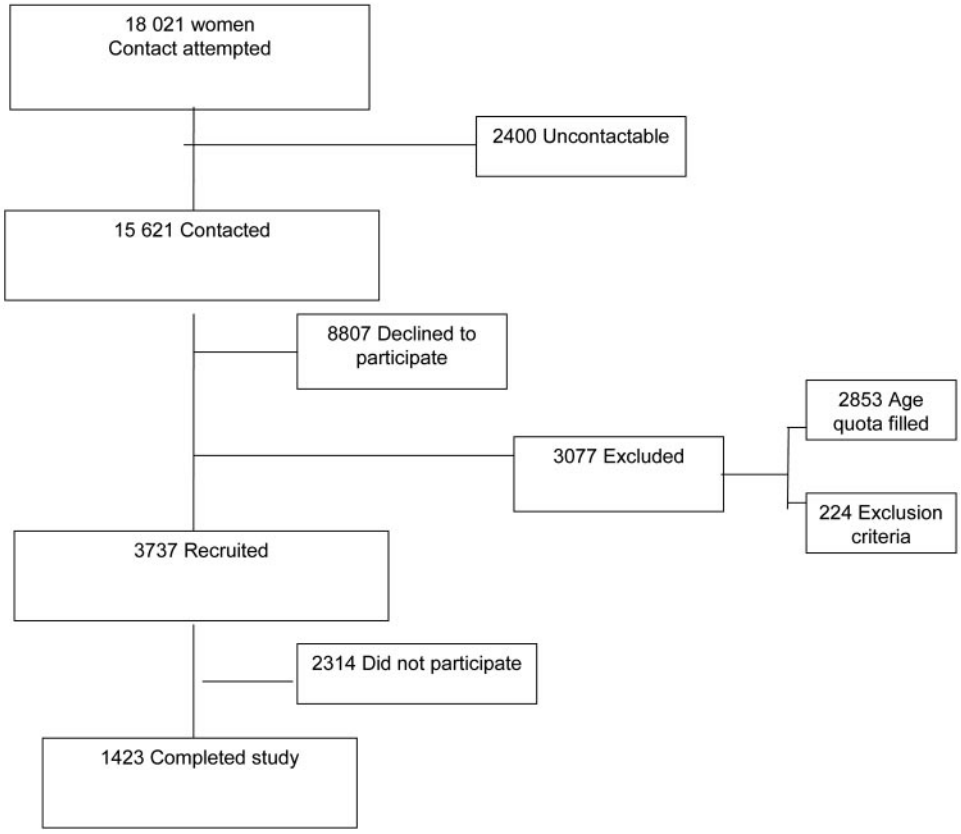

FIG. 1. Flow of study participants.

indicates a decline by 55% between the youngest and oldest groups. Similar comparisons between the two extremes of age demonstrated a fall in mean free T by 49%, a fall in mean DHEAS by 77%, and a fall in mean androstenedione by 64%. The regression coefficients for age in linear regression models for each androgen level are negative and significantly different from zero ($P < 0.001$). The r^2 values indicate that age explains between 30.8% (DHEAS) and 12.1% (free T) of the variation seen in the serum levels of the hormones. SHBG does not appear to vary over the first five decades of adult life and increases minimally in the age group 65–75 yr (Fig. 3). A Lowess curve was used to describe the changes in SHBG in later years that would not be captured by a linear model.

TABLE 1. Characteristics of the total study population and the reference group

	All women (n = 1423)	Reference group (n = 595)
Age (yr)		
18–24	5.1	3.7
25–34	13.8	16.3
35–44	19.8	25.7
45–54	22.6	23.5
55–64	19.7	12.4
≥65	19.0	18.3
Weight (kg)	73.4 (17.0)	72.9 (18.0)
BMI (kg/m^2)	27.8 (6.5)	27.4 (6.9)
Cigarette smoking		
Nonsmoker	84.6	83.0
Current smoker	15.4	17.0
Parity		
Never pregnant	16.2	17.1
One or more children	79.5	78.2

Data represent percent of total or mean (SD).

When a quadratic term, age^2, is added to each regression model, the proportion of total variation explained by the regression model increases and ranges from 31.5% for DHEAS down to 15.1% for free T. Coefficients for the quadratic terms were significantly different from zero, indicating that a linear model, restricted to age alone, is not the best fit for the data and that the rate of decline in androgen levels diminishes in older women. The regression models that include both the age and age^2 terms predict that DHEAS continues to decline over the full age range studied, with the lowest level predicted for the oldest women in the sample aged up to 75 yr. The model for androstenedione predicts a nadir at 71 yr with a small increase between 71 and 75 yr. The model for total T predicts a nadir between 62 and 63 yr of age and the model for free T predicts a nadir between 64 and 65 yr of age.

We investigated whether menopause makes a contribution to the determination of androgen levels independent of age. The inclusion of a dichotomous term for menopausal status in the regression equations for the serum levels of the androgens does not improve the proportion of the variation explained, and the regression coefficient for the menopause term was never significant at the 5% level. Plots of the levels of each of the steroids for premenopausal (n = 88) and postmenopausal (n = 52) women by individual year of age between 45 and 54 yr indicates that there is no apparent difference between women who are pre- or postmenopausal at any age in this interval (Fig. 4).

TABLE 2. Values for androgens by decade for the reference group

	Age grouping (yr)					
	18–24	25–34	35–44	45–54	55–64	65–75
n	22	97	153	140	74	109
Total T (nmol/liter)						
Mean	1.58	1.11	0.92	0.81	0.66	0.71
Median	1.55	1.00	0.80	0.70	0.55	0.60
SD	0.55	0.45	0.45	0.41	0.40	0.48
Minimum	0.60	0.30	0.10	0.10	0.10	0.10
10th centile	0.86	0.58	0.50	0.40	0.20	0.30
90th centile	2.47	1.70	1.40	1.30	1.25	1.10
Maximum	2.90	2.30	3.20	2.60	2.00	4.00
Free T (pmol/liter)						
Mean	23.61	17.25	13.67	11.82	10.81	9.76
Median	20.52	15.27	12.36	9.87	8.31	8.75
SD	10.44	9.70	7.43	7.68	8.01	6.92
Minimum	5.77	3.02	1.55	1.81	2.03	1.36
10th centile	12.91	8.17	5.80	5.25	3.69	3.43
90th centile	38.64	31.70	23.52	21.28	20.88	17.26
Maximum	46.32	58.24	47.92	43.60	49.28	52.87
DHEAS (μmol/liter)						
Mean	7.49	4.72	4.31	3.42	2.36	1.76
Median	7.30	4.50	3.90	2.85	2.15	1.50
SD	2.63	2.08	2.11	2.01	1.57	1.40
Minimum	4.00	0.90	0.80	0.30	0.30	0.30
10th centile	4.03	2.20	1.86	1.30	0.70	0.50
90th centile	10.78	7.90	7.31	6.20	5.30	3.10
Maximum	14.90	11.20	12.50	12.00	6.20	8.00
Androstenedione (nmol/liter)						
Mean	8.46	6.44	5.15	4.17	3.14	3.07
Median	7.95	6.30	4.50	3.80	2.80	2.80
SD	3.09	2.46	2.39	2.14	1.76	1.86
Minimum	4.40	1.70	1.60	1.20	0.50	0.50
10th centile	4.86	3.00	2.64	2.00	1.30	1.30
90th centile	13.72	9.46	8.48	6.29	5.10	5.40
Maximum	14.70	14.80	18.80	16.50	10.60	11.80

To convert nmol/liter to ng/dl or pmol/liter to pg/dl, divide by 0.0347; to convert μmol/liter to μg/dl, divide by 0.027.

Comparing oophorectomized women with reference-group women in the age group 55–64 yr, total T levels are 0.38 (0.26) nmol/liter [mean (SD)] and 0.66 (0.40) nmol/liter, respectively ($P = 0.02$), and mean free T levels are 5.54 (4.40) and 10.81 (8.01) pmol/liter, respectively ($P = 0.04$) (Table 3). Similarly, for the age group 65–75 yr, total T levels are 0.39 (0.22) and 0.71 (0.48) nmol/liter ($P = 0.01$), and free T levels are 6.06 (3.33) and 9.76 (6.92) pmol/liter ($P = 0.04$) for oophorectomized *vs.* reference-group women, respectively. Although there is a trend toward lower levels, there are no statistically significant differences in DHEAS or androstenedione between oophorectomized women aged 55–75 yr and women in the reference group. We examined our data for evidence that hysterectomy or tubal ligation are each associated with differences in serum levels of androgens. The differences between groups of women who did and did not report these procedures did not achieve statistical significance at the 5% level but suggested a decline in all androgens with each of these procedures.

Discussion

We report a decline in total and calculated free T, DHEAS, and androstenedione with age, with no corresponding change in SHBG. The decline in each steroid is steepest in the early reproductive years, with a flattening out in midlife and

TABLE 3. Effect of oophorectomy on androgens in older women

	Mean (SD), oophorectomized women	Mean (SD), reference women	Mean difference	95% CI for mean difference	*P* value
55–64 yr, oophorectomized, n = 11; reference, n = 74					
Total T (nmol/liter)	0.38 (0.26)	0.66 (0.40)	−0.27	−0.52, −0.03	0.029
Free T (pmol/liter)	5.54 (4.40)	10.81 (8.01)	−5.27	−10.20, −0.34	0.037
DHEAS (μmol/liter)	1.89 (1.50)	2.37 (1.57)	−0.48	−1.48, 0.53	0.347
Androstenedione (nmol/liter)	2.15 (1.28)	3.14 (1.76)	−1.0	−2.10, 0.10	0.075
65–75 yr, oophorectomized, n = 16; reference women, n = 109					
Total T (nmol/liter)	0.39 (0.22)	0.71 (0.48)	−0.32	−0.56, −0.07	0.011
Free T (pmol/liter)	6.06 (3.33)	9.76 (6.92)	−3.70	−7.19, −0.21	0.038
DHEAS (μmol/liter)	1.13 (0.64)	1.76 (1.40)	−0.63	−1.33, 0.08	0.081
Androstenedione (nmol/liter)	2.93 (2.00)	3.07 (1.86)	−0.14	−1.14, 0.86	0.782

To convert nmol/liter to ng/dl or pmol/liter to pg/dl, divide by 0.0347; to convert μmol/liter to μg/dl, divide by 0.027. CI, Confidence interval.

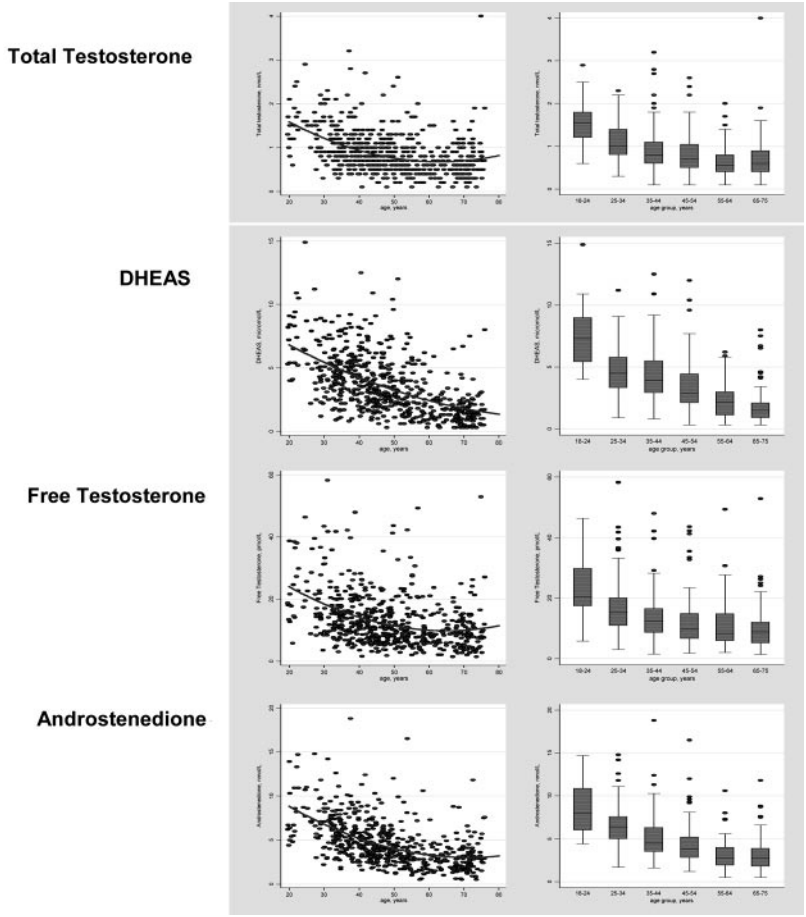

FIG. 2. Relationship between age and individual androgens for the reference group. To convert nmol/liter to ng/dl or pmol/liter to pg/dl, divide by 0.0347; to convert μmol/liter to μg/dl, divide by 0.027. Raw data are represented as scatter graphs with fitted regression curves. In the *box and whisker plots*, the *box* represents the interquartile range, and the *line in the box* is the median. The *whiskers* extend to the upper and lower adjacent values. The upper adjacent value is defined as the largest data point less than or equal to the 75th percentile + 1.5 × interquartile range. The lower adjacent value is defined as the smallest data point greater than or equal to the 25th percentile − 1.5 × interquartile range. Outliers are any values beyond the *whiskers*.

a tendency for a small increase in the later years. An effect of natural menopause on circulating androgen levels was not seen, contrasting with the sharp decline in estradiol that occurs at this time.

To explore normal physiology, we eliminated the effects of factors known to modulate androgen levels in women and thus achieved a reference group of 595 women for this study, derived from a large group of non-healthcare-seeking women recruited from the community. Over 3000 women agreed to participate in this study; however, 1423 women completed the study, most likely because of the requirement for attendance at a pathology laboratory for a fasting, morning blood sample (measurement of lipid profiles was a subproject of this study) and completion of questionnaires of a personal nature. Although a large number of younger women agreed to participate in this study, relatively few completed the study, most likely because of the inconvenience of having to attend for a fasting blood sample linked to menstrual cycle phase. A high nonparticipation rate is a price paid for population-based recruitment. A convenience sample could have been used to improve the participation rate but could also have biased the results. Our sample being mostly Caucasian is reflective of the Australian population. It remains to be established whether our findings reflect the changes in women of differing ethnicity.

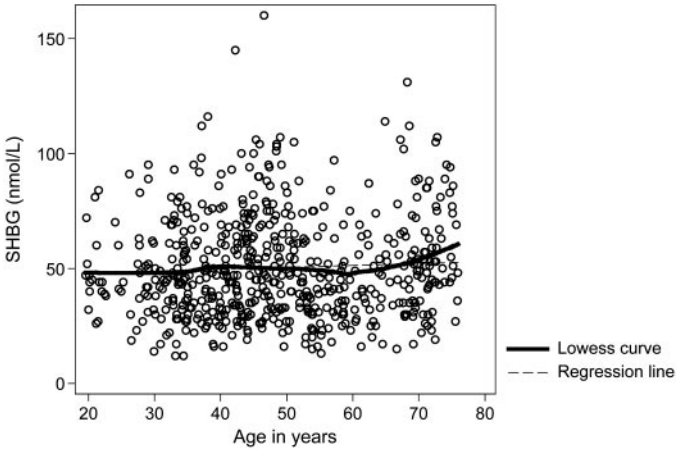

FIG. 3. Relationship between age and SHBG in the reference group. See text for definition of Lowess curve.

Several women in the reference group had androgen levels that would suggest pathophysiological androgen excess. These women denied use of androgenic steroid hormone preparations and had no history of acne, hirsutism, or PCOS, and we could find no reason to exclude them from the analysis. These observations reconfirm that even within a so-called normal population there is a wide range of normality.

The decline in free and total T in the early premenopausal years that we have reported is not novel. Zumoff *et al.* (1) reported lower mean 24-h values for total and calculated free T among older *vs.* younger reproductive aged women (n =

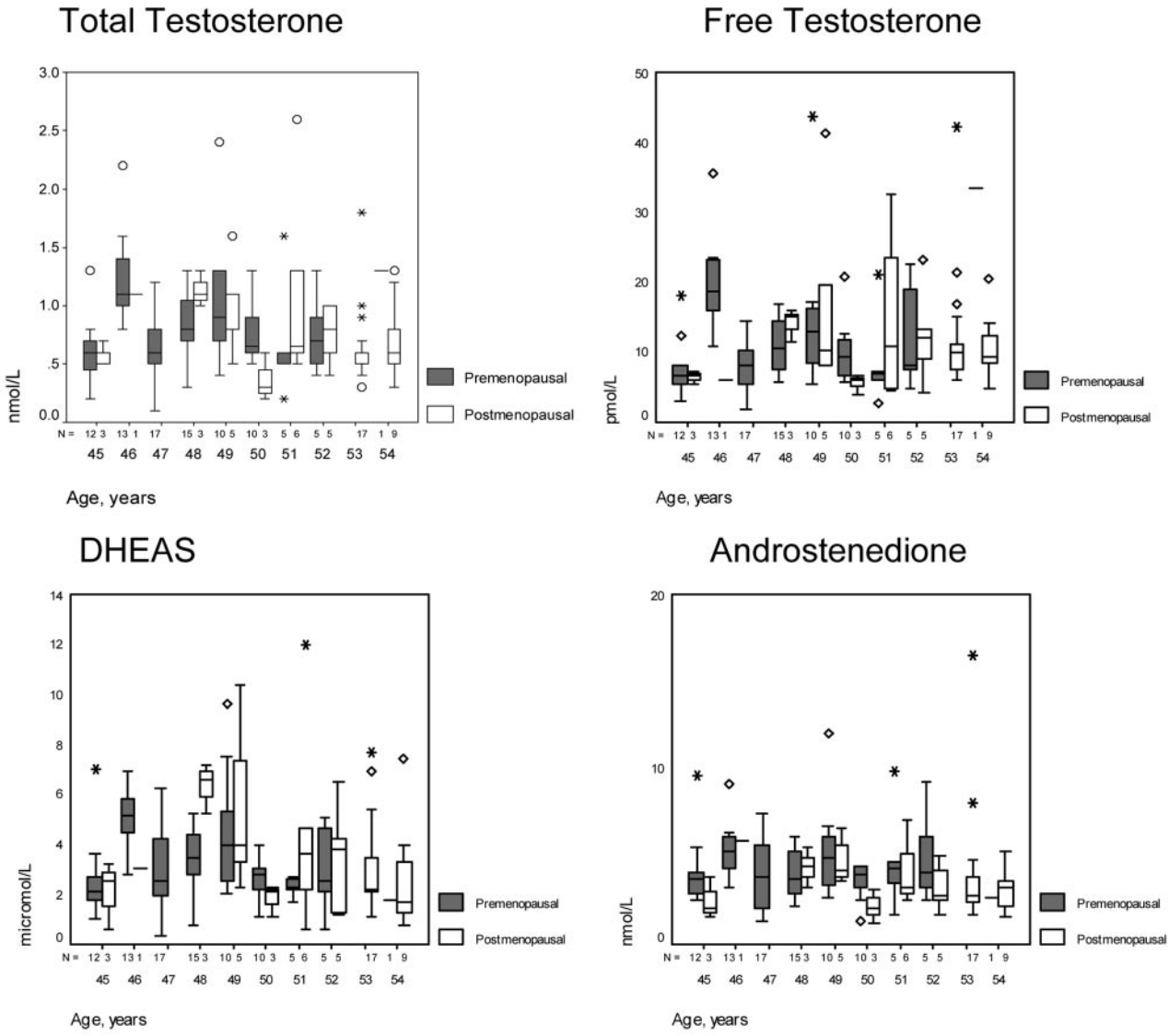

FIG. 4. Androgen levels for premenopausal and postmenopausal women in the reference group between 45 and 54 yr. To convert nmol/liter to ng/dl or pmol/liter to pg/dl, divide by 0.0347; to convert μmol/liter to μg/dl, divide by 0.027.

33 women), and others have reported loss of the midcycle rise in free T that characterizes the menstrual cycle in young ovulating women in the later reproductive years (9). However, this is the first study to demonstrate the early age-related decline of total T, free T, DHEAS, and androstenedione in the context of the full adult female life span. The extent to which this decline reflects aging ovarian function or the decline in adrenal precursor steroids needs to be determined.

When we compared hormone levels between premenopausal and postmenopausal women of the same age, there was no effect of the menopause transition. Rather, the higher androgen levels in premenopausal compared with postmenopausal women in this reference group reflects the strong effect of age. This is in keeping with previous data (10).

Whether the postmenopausal ovary has significant endocrine activity is somewhat controversial. Reductions in T and androstenedione have been demonstrated after oophorectomy (11, 12), although more recently, Couzinet *et al.* (13) reported that the postmenopausal ovary is not a source of significant androgen production. This study indicates lower levels of total and free T, but not DHEAS or androstenedione, among older postmenopausal women with previous bilateral oophorectomy, suggesting ongoing ovarian production of androgens many years beyond the time of natural menopause. In addition, a late elevation in total and calculated free T and androstenedione was suggested by the regression models within the reference group, consistent with previous reports (14–16). This cannot be explained by changing SHBG levels but may represent an increase in ovarian androgen production via stimulation of ovarian theca cells by elevated levels of LH long after the menopause. We were not able to comment on the difference between androgen levels in oophorectomized *vs.* reference-group women younger than 55 yr, because of insufficient numbers of younger oophorectomized women in this community-based sample.

The decline of adrenal DHEA and DHEAS with age that we have observed has been described by others (2, 17), but the mechanism underlying this is unclear. An alteration in adrenal zonation, such that the zona reticularis is of lesser mass with advancing age, has been described (18). Additional studies are necessary to determine the cause and mechanism of the seemingly selective loss of zona reticularis mass and to confirm this process occurs with both female and male aging.

The slightly higher SHBG levels seen in the oldest women in this study contrasts with the findings of Burger *et al.* (5), who reported a decrease across the menopause transition, and also with Gambera *et al.* (19), who reported a decline in SHBG levels with advancing age. Maruyama *et al.* (20) reported an increase in SHBG with age, such that levels in women in their 80s were double those of women in their 20s. The larger number of women in this study compared with the other studies may explain the difference in findings for SHBG.

Our findings of a statistically nonsignificant decline in androgen levels after hysterectomy and tubal ligation is in keeping with the findings of Laughlin *et al.* (14–16), who reported significantly lower levels of androstenedione and total T in women who had previously undergone hysterectomy, although this study was restricted to women aged 50–89 yr.

This study provides normative data for the specific assays used and for free T levels calculated using the Sodergard equation. Levels of free T calculated using this equation have been demonstrated to correlate strongly with levels measured by equilibrium dialysis (7, 21, 22). Because measurements vary between assays as a result of methodology and the antibodies employed, these values should not be considered absolute but rather a guide to the degree of change one would expect to observe using other validated methods. Because of the cross-sectional design of this study, we cannot be certain that the changes we have described occur in any given individual with age, although this is highly probable. The collection of prospective, longitudinal data would require much greater numbers, because it would be limited by common medical and surgical interventions, and would be a major undertaking in terms of logistics, cost, and compliance.

In summary, serum androgen levels decline with age from the early reproductive years, do not vary with the menopause transition, and with the exception of the preandrogen DHEAS, increase slightly during the seventh decade.

From a clinical perspective, this report provides physiological reference ranges that are an essential basis for further investigation into female androgen insufficiency or excess.

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