0021-972X/00/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 85, No. 8
Printed in U.S.A.

A Prospective Longitudinal Study of Serum Testosterone, Dehydroepiandrosterone Sulfate, and Sex Hormone-Binding Globulin Levels through the Menopause Transition*

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ABSTRACT

The aims of this study were to describe, in relation to date of final menses, the average androgen levels of women in the years before and after this date, and to determine the extent to which these average levels were dependent on age and body mass index (BMI) and the degree of tracking in residual androgen levels, or the extent to which individuals above (below) the mean for their age or time relative to final menstrual period (FMP) and BMI remain above (below) the mean as time progresses. Serial levels of serum sex hormone-binding globulin (SHBG), testosterone (T), and dehydroepiandrosterone sulfate (DHEAS) were measured annually in 172 women from the Melbourne Women's Midlife Health Project who experienced a natural menopause during 7 yr of follow-up. Fasting blood samples were drawn between days 4–8 if women were still menstruating or after 3 months of amenorrhea. The free androgen index (FAI) was calculated as the ratio of T to SHBG × 100. Means of the log-transformed androgen levels were analyzed as a double logistic function of time relative to FMP as well as age and BMI, and correlations between repeated androgen levels were measured. Mean SHBG levels decreased by 43% from 4 yr before to 2 yr after the FMP. The time of most change was 2 yr before FMP [95% confidence interval (CI), 0.8–3.2]. SHBG levels were, on the average, 5% lower for each halving of estradiol (E_2) levels and 4% lower for each kilogram per m^2 of BMI ($P < 0.0001$). About one third of the decline in SHBG was explained by E_2 and BMI. After adjusting for all variables, SHBG showed strong tracking. Mean T levels did not vary with time relative to FMP and were independent of age and BMI. Residual values of T showed weak tracking. The FAI increased by 80% from 4 yr before FMP to 2 yr after FMP, and changed maximally 2.2 yr before FMP (95% CI, 1.2–3.2). The FAI was not related to age or E_2, but was, on the average, 4% higher for each kilogram per m^2 of BMI ($P < 0.0001$). Residual values of FAI showed moderate tracking. Mean DHEAS levels were not related to the FMP, but were 1.5% lower for each year of age ($P < 0.01$) and 3.8% lower for each kilogram per m^2 of BMI ($P < 0.0001$). Residual values of DHEAS showed strong tracking. It is concluded that SHBG and FAI levels change at the time of the menopause, at least partially due to the decline in E_2. DHEAS decreases as a function of age, not time relative to FMP, and T remains unchanged during the menopausal years. SHBG and DHEAS show a high degree of stability within an individual over time. (*J Clin Endocrinol Metab* **85:** 2832–2838, 2000)

THE MAJOR HORMONAL changes associated with the occurrence of the final menstrual period (FMP) in normal subjects include a profound fall in circulating estradiol (E_2), primarily of ovarian origin, beginning up to about 1 yr earlier, and an accompanying large increase in the circulating gonadotropins, FSH and LH (1, 2). Changes in circulating androgens are more complex. In cross-sectional studies, levels of testosterone (T) have been reported to be lower in postmenopausal than premenopausal women (3, 4), whereas in the few longitudinal studies, either no change (5) or a small fall, on the order of 15% (2), in total T has been reported. T has been demonstrated to be derived approximately equally from direct adrenal and ovarian secretion (6), each organ contributing approximately 50 μg/day or about 25% of the plasma level, with the remaining 50% being derived from the peripheral conversion of androstenedione, again produced approximately equally by the adrenal and the ovary (6). The major adrenal androgen, dehydroepiandrosterone sulfate (DHEAS), reaches its peak levels in young women in their 20s and declines progressively thereafter, with no obvious relationship to the menopause (7), although ovarian factors may exert some influence on its levels (8).

The Melbourne Women's Midlife Health Project (9, 10) is a prospective study of biological and lifestyle-related factors associated with the menopause transition in a cohort of middle-aged Australian-born women recruited by random digit telephone dialing from the Melbourne community. It has provided the opportunity to examine longitudinally, levels of total T, sex hormone-binding globulin (SHBG), the calculated free androgen index (FAI), and DHEAS with time relative to final menses, age, and body mass index (BMI).

Received October 29, 1999. Revision received April 19, 2000. Accepted May 14, 2000.

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* The Melbourne Women's Midlife Health Project is supported by grants from the Victorian Health Promotion Foundation and the Public Health Research and Development Committee of the Australian National Health and Medical Research Council and the Australasian Menopause Society. Support for the hormone assays has also been provided by Organon Australia Pty. Ltd.

Subjects and Methods

The present study is based on data collected from the first 7 yr of the Melbourne Women's Midlife Health Project (9, 10). In 1991, a sample of 2001 Melbourne women, aged 45–55 yr, was recruited by random digit telephone dialing. A subcohort of 438 premenopausal women was then invited into a longitudinal study, which entailed annual interviews and an annual blood sample, so that their menopausal experiences and hormonal changes could be documented. To be eligible to participate in the longitudinal study, a woman had to have at least 1 intact ovary, to not be taking hormone therapy, and to have menstruated within the last 3 months. A comparison of participants *vs.* eligible nonparticipants in the longitudinal study has been reported (10). The longitudinal study commenced in 1991, and this paper reports on 7 yr of data collected up until 1998.

Final menstrual period

A woman's menstrual history during her transition to menopause was documented using menstrual calendars. The calendars were completed between interviews and recorded details of each menstrual period. The day of a woman's final menstrual period (FMP) was defined retrospectively after 12 consecutive months of amenorrhea.

Hormonal assays

Fasting blood samples were drawn between the fourth and eighth days of the menstrual cycle in regularly cycling women or after 3 months of amenorrhea. SHBG and DHEAS were measured by automated enzyme immunoassay using the Immulite system purchased in kit form from Diagnostic Products (Los Angeles, CA). T and E_2 were measured as described previously (10). The FAI was calculated as the ratio of the measured T to measured SHBG $\times$ 100. Samples below assay sensitivity were given the value of assay sensitivity: E_2, 20 pmol (n = 343; 33%); and T, 0.1 nmol (n = 3,0.3%).

Study sample

The present report is based on those 172 women who had experienced a natural menopause and provided at least 1 blood sample during follow-up and for whom the date of FMP was recorded. Excluded were women who experienced surgical menopause through hysterectomy, bilateral oophorectomy, or endometrial or iatrogenic ablation or who took hormone therapy before the cessation of menses. For women who took hormone therapy after their FMP, all observations taken during hormone therapy were excluded.

Statistical analysis

The women experienced menopause at varying times in the 7 yr of follow-up. By aligning each measurement from a woman according to the date of her FMP, we were able to summarize the accumulated androgen data over a 12-yr time scale (from 5 yr before to 7 yr after FMP).

Modeling of log(SHBG), log(T), log(FAI), and log(DHEAS) as a function of time to menopause

The longitudinal data were analyzed as repeated measures ordered by time relative to FMP (t), taking into account any correlation between successive observations within individuals. The hormone values were transformed by natural logarithm before analysis to ensure that the distributions of the residuals (observed values − fitted values) were close to normal. The statistical package FISHER (11) was used to model the means of the log-transformed hormone levels, μ, as a function of time, t (measured in years), according to the double logistic equation: $\mu(t) = h_1 - 2(h_1 - h_\theta)/\{\exp[\lambda_0(t-\theta)] + \exp[\lambda_1(t-\theta)]\} + \beta_1 age + \beta_2 BMI + \beta_2 \log(E_2)$, where θ is the approximate time of maximum rate of change, h_1 is the maximum mean, h_θ is the mean at approximate time of maximum change, and λ_0 and λ_1 are parameters representing rates of change (12, 13). Similar methodology was used in a previous analysis of hormone levels (14). The double logistic model was compared with a straight line regression model using the Akaike information criteria (15). The regression coefficients, β_1, β_2, and β_3, represent the linear effects of age, BMI, and log(E_2), respectively, when adjusting for time relative to FMP. Results are presented from the best fitting model only. The correlation between the residual repeated measures after adjusting the mean for time and possibly age, BMI, and log(E_2) was estimated as a function of the absolute time between repeated measures, $t_j - t_k$, where t_j and t_k represent the times of measures, and is a measure of the tracking of androgen levels in an individual about the fitted mean. Tracking refers to the extent to which individuals above (below) the fitted mean remain above (below) the mean as time progresses, where a value of 1 means they move parallel to the fitted mean, and 0 means they vary randomly about the fitted mean.

Results

The mean age of the 172 women at baseline was 49.1 $\pm$ 2.4 ($\pm$SD), and over the study period the age range was from 46–62 yr. Seventy-nine percent of the cohort were married or living with a partner, and 69% were in the paid workforce (full or part time). Of those employed, 65% were involved in sales, white collar, executive, self-owned businesses, or professional roles. The median parity was 3 (range, 0–4). The median age at FMP was 52 yr and ranged from 46–58 yr.

During follow-up, a total of 1046 blood samples were taken (average, 6.1/woman). Sixty-four percent of women contributed a complete set of 7 blood samples. Table 1 shows the median values and normal ranges of the androgen levels, as defined by the 5th and 95th percentiles, pre- and post-FMP, and for all samples combined.

Modeling of SHBG

The double logistic model provided a better fit than the linear regression model ($P < 0.0001$), and the estimates are presented in Table 2. Figure 1A shows the fitted curve against time relative to FMP. Mean SHBG levels decreased gradually, from 83.8 nmol/L at −4 yr to 54.5 nmol/L at the FMP and further to 47.7 nmol/L at +2 yr, representing a 43% decrease over 6 yr. The time of maximum change was estimated to be 2 yr before FMP [95% confidence interval (CI), 0.8–3.2]. We added other variables to the model and found that SHBG was negatively associated with BMI [$\beta = -0.039$; SE(β) = 0.004; $P < 0.0001$] and positively associated with log(E_2) [$\beta = 0.069$; SE(β) = 0.010; $P < 0.0001$]. After adjusting for these covariates, the fitted curve (Fig. 1B) appeared flatter; there was only a 29% decline over 6 yr, and the decline was more abrupt between −4 and −2 yr. About one third of the

TABLE 1. Median and normal range (5th percentile to 95th percentile) for SHBG, T, FAI, and DHEAS in samples taken pre-FMP and post-FMP and in all samples combined

	Pre-FMP (median age, 51 yr)	Post-FMP (median age, 54 yr)	Pre- and post-FMP (median age, 53 yr)
SHBG (nmol/L)	62.1 (22.7–145.1)	50.5 (21.0–99.8)	53.4 (22.0–118.9)
T (nmol/L)	1.4 (0.6–2.4)	1.4 (0.6–2.4)	1.4 (0.6–2.4)
FAI (no units)	2.2 (0.8–7.4)	2.7 (1.0–6.9)	2.5 (0.9–7.0)
DHEAS (μmol/L)	2.0 (0.8–4.8)	1.9 (0.8–4.4)	1.9 (0.8–4.5)

TABLE 2. Parameter estimates (SEs in *parentheses*) for the double logistic models for mean log(SHBG) and log(FAI) before (i) and after (ii) adjusting for covariates

Parameter	Log(SHBG)		Log(FAI)	
	Model i	Model ii	Model i	Model ii
Double logistic model				
h_1 (maximum mean)	4.54 (0.12)	5.00 (0.14)	0.392 (0.138)	−0.578 (0.171)
θ (time at maximum growth rate)	−1.98 (0.56)	−2.28 (0.36)	−2.23 (0.51)	−2.07 (0.438)
h_θ (mean at maximum growth time)	4.22 (0.07)	4.88 (0.13)	0.636 (0.071)	−0.372 (0.150)
λ_0 (rate of change parameter)	−0.76 (0.31)	−2.11 (1.36)	−1.57 (1.16)	−1.89 (1.52)
λ_1 (rate of change parameter)	−0.030 (0.033)	−0.066 (0.025)	−0.050 (0.030)	−0.054 (0.030)
Covariates				
β_1 (coefficient for age)				
β_2 (coefficient for BMI)		−0.039 (0.004)		0.040 (0.005)
β_3 [coefficient for log(E_2)]		0.069 (0.010)		
Covariance parameters				
σ_r^2	0.195 (0.021)	0.137 (0.015)		
λ	0.033 (0.009)	0.033 (0.011)		
σ_i^2			0.177 (0.023)	0.127 (0.018)
σ_e^2	0.054 (0.004)	0.053 (0.004)	0.188 (0.009)	0.187 (0.009)

decline in mean SHBG levels was explained by adjusting for E_2 and BMI. Figure 2 shows the negative linear association between log(SHBG) and BMI. Correlations between repeated measures of SHBG were strong within a subject and decreased minimally over time, from r = 0.7 for measures taken 1 yr apart to r = 0.6 for measurements taken 6 yr apart (see Fig. 7a).

Modeling of T

The linear regression model provided the best fit (see Table 3 for the parameter estimates). Mean levels of T (~1.4 nmol/L) did not vary across the observed 12-yr time scale [$\beta = -0.003$; SE(β) = 0.003; $P > 0.05$]. The fitted model is presented in Fig. 3. T was also not related to age [$\beta = -0.0011$; SE(β) = 0.0021; $P > 0.05$], BMI [$\beta = -0.0022$; SE(β) = 0.0052; $P > 0.05$], or log(E_2) [$\beta = 0.0259$; SE(β) = 0.0721; $P > 0.05$]. Repeated measures of T were weakly correlated within a subject (r = 0.25), and this correlation was independent of the time between measurements (see Fig. 7b).

Modeling of FAI

The double logistic model provided a better fit than the linear regression model ($P < 0.0001$; see Table 2 for the corresponding estimates and Fig. 4 for the fitted curve). Mean levels of the FAI increased with time relative to FMP by 80% over 6 yr; from 1.5 at −4 yr to 2.7 at +2 yr. The time of maximum change was estimated to be 2.2 yr before the FMP (95% CI, 1.2–3.2). The FAI was also positively associated with BMI, with an average increase of 4% for each unit increase in BMI ($P < 0.0001$). The FAI was not related to either age or E_2 after allowing for the other two factors. The correlations between repeated measures of the FAI were moderately strong within a subject (r = 0.4) and independent of time between measurements (see Fig. 7c).

Modeling of DHEAS

Linear regression provided the best fit (see Table 3 for the parameter estimates and Fig. 5, a and b). Mean levels of DHEAS were not related to the FMP [$\beta = 0.014$; SE(β) = 0.019; $P > 0.05$], but decreased with age [$\beta = -0.015$; SE(β) = 0.005;

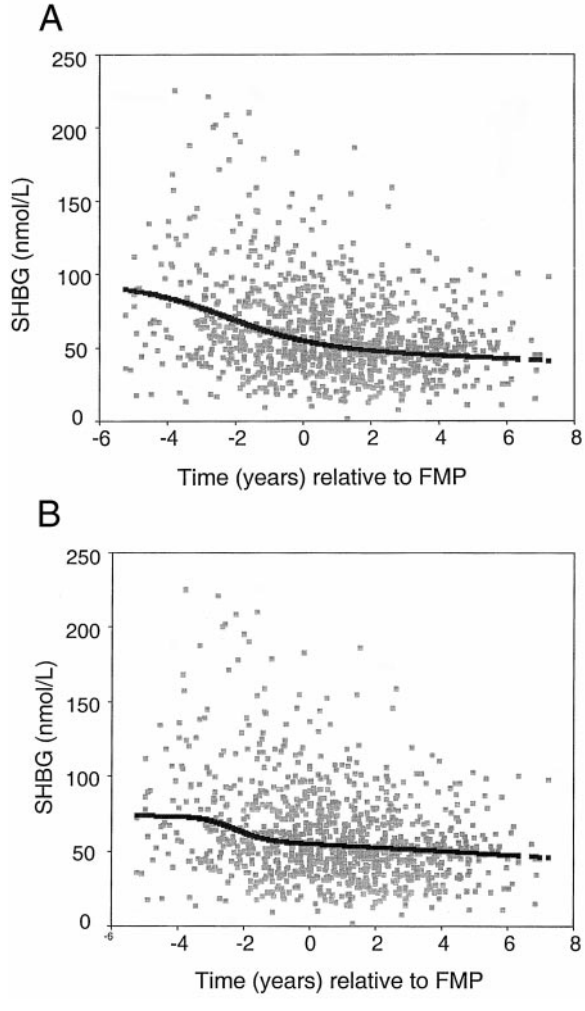

FIG. 1. Double logistic model: observed SHBG and fitted levels of mean SHBG across the menopausal transition before (A) and after (B) adjusting for levels of BMI and log(E_2). The *horizontal axis* represents time (years) with respect to FMP (0); negative (positive) numbers indicate time before (after) FMP. The fitted line in B uses median values for E_2 (40) and BMI (25).

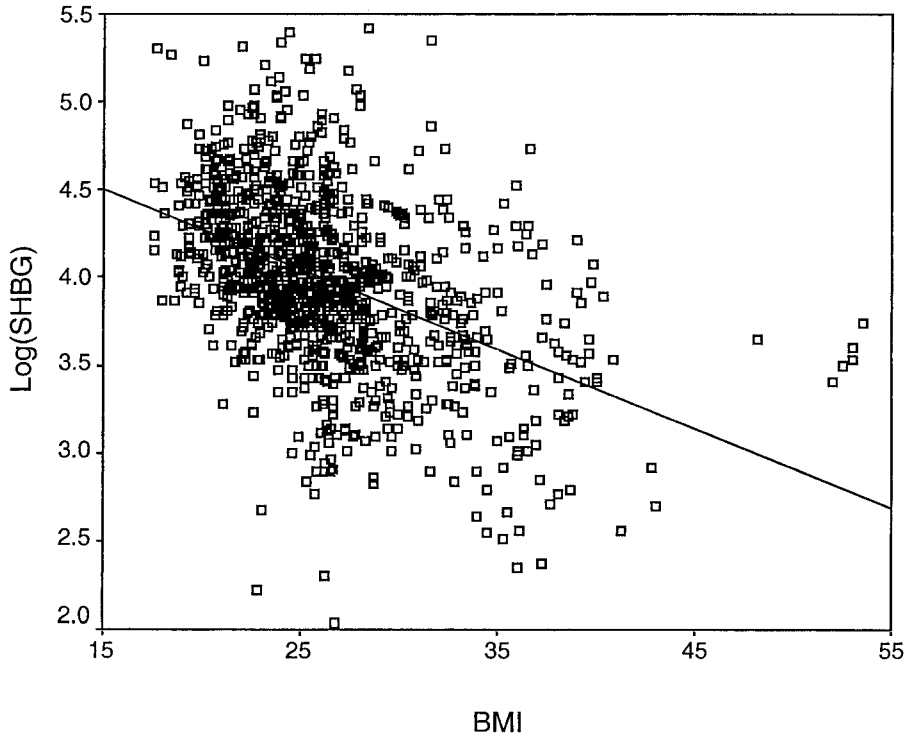

FIG. 2. Scatterplot of log(SHBG) *vs.* BMI. r = −0.45; $P < 0.0001$.

TABLE 3. Parameter estimates (SEs in *parentheses*) for the linear regression models for mean log(DHEAS) and log(T) before (i) and after (ii) adjusting for covariates

Parameter	Log(T),[a] model i	Log(DHEAS)	
		Model i	Model ii
Linear regression model			
Intercept	1.17 (0.012)	0.669 (0.044)	3.03 (1.01)
β_0 (coefficient for t)	−0.003 (0.003)	−0.026 (0.005)	0.014 (0.019)
Covariates			
β_1 (coefficient for age)			−0.015 (0.005)
β_2 (coefficient for BMI)			−0.038 (0.019)
β_3 [coefficient for log(E_2)]			
Covariance parameters			
σ_r^2		0.280 (0.032)	0.271 (0.031)
λ		0.014 (0.005)	0.013 (0.005)
σ_i^2	0.015 (0.002)		
σ_e^2	0.043 (0.002)	0.028 (0.003)	0.028 (0.003)

[a] Model ii for log(T) is omitted from this table, as none of the covariates were related to T.

$P < 0.05$] and BMI [$\beta = -0.038$; SE(β) = 0.019; $P < 0.05$]. These estimates correspond to a 1.5% decrease for each year of age and a 3.8% decrease for each unit increase in BMI. Figure 6 shows the negative linear association between log(DHEAS) and BMI. Repeated measures of DHEAS within a given subject were highly correlated over time (r = 0.9 for 1 yr apart; r = 0.8 for 6 yr apart; see Fig. 7d).

Discussion

The present report describes analyses of circulating androgen measurements from annual blood samples taken in a prospective longitudinal study of 172 women recruited from the general community (10). The date of FMP was defined retrospectively and established on the basis of menstrual diaries kept by the women themselves. For cycling women, blood samples were taken during the early to mid-follicular phase of the cycle (between days 4 and 8). The overall data gave a 12-yr perspective from 5 yr before to 7 yr after FMP. We found that the levels of total serum T were unchanged across the menopausal transition, despite having the statistical power to detect effects of 1%/yr or more. T was also independent of age and BMI.

Previous cross-sectional studies suggested that a fall in total T occurs across the menopause. For example, Rozenberg *et al.* (4) reported T levels in 449 women aged 40 yr and over, without reporting their menopausal status. Mean T levels were significantly higher in the subjects aged 41–50 yr than in those aged 51–60 yr; the actual values derived by inspection of their data indicated a fall from 1.01 nmol/mL to approximately 0.80 nmol/L. Long-

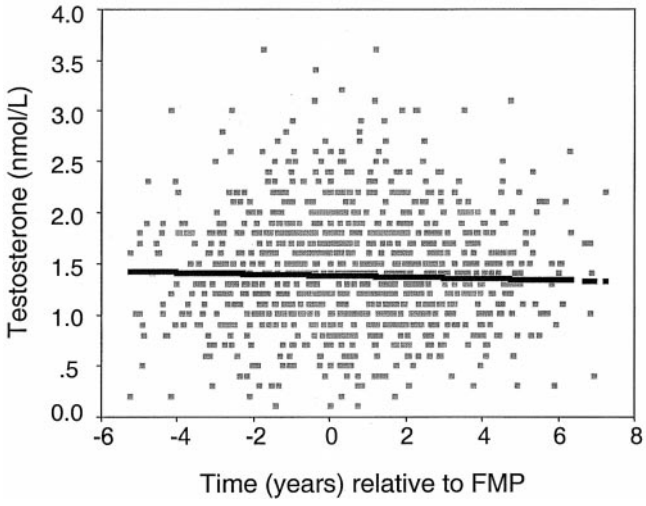

FIG. 3. Linear regression model: observed T and fitted levels of mean T across the menopausal transition. The *horizontal axis* represents time (years) with respect to FMP (0); negative (positive) numbers indicate time before (after) FMP.

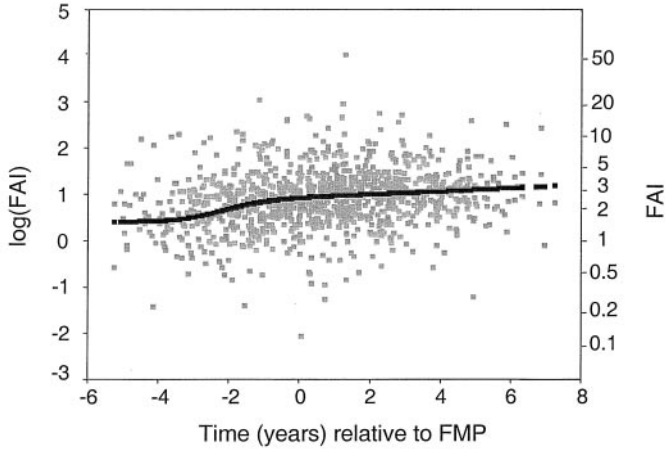

FIG. 4. Double logistic model: observed FAI and fitted levels of mean FAI across the menopausal transition. The *left* and *right axes* show FAI levels on the log and antilog scales, respectively. The *horizontal axis* represents time (years) with respect to FMP (0); negative (positive) numbers indicate time before (after) FMP.

cope *et al.* (5) studied 88 women, aged 45–58 yr, who were within 1 month of FMP or up to 76 months later. No change in total T was observed over that period. In their discussion these researchers referred to the fact that the total T levels in their study (mean ± SE, 0.62 ± 0.02 nmol/L) were significantly less than those in a group of normal women sampled on days 5–7 of their cycle (1.01 ± 0.07 nmol/L). The ages of this group of normal women were not specified. Bancroft and Cawood (3) studied 141 women aged 40–60 yr, each sampled on 4 occasions at weekly intervals. The mean total T level in the postmenopausal group (n = 54), 0.71 nmol/L, was significantly lower than that in their cycling group of subjects (n = 49; 0.97 nmol/L). Thus, from cross-sectional studies it has been inferred that the menopause is associated with a fall in total T levels. In our own preliminary analysis of cross-sectional data obtained in the first year of our study, no significant change in total T was observed with changing menopausal status from regularly cycling to postmenopausal (10). One previous prospective longitudinal study (2) reported a 15% fall in total T, comparing mean levels in 20 subjects, a very small sample size. It is of interest that Ushiroyama and Sugimoto (16) observed no change in the ovarian venous concentrations of T when postmenopausal women were compared with premenopausal women.

It is noteworthy that an earlier study had reported a major fall in both total and free T in normal premenopausal women (17). Investigators in that study sampled 33 healthy, regularly cycling, nonobese women, aged 21–51 yr, and calculated that the expected T concentration in a 40-yr-old woman would be 0.61 nmol/L, approximately 50% that in a 21-yr-old woman (1.3 nmol/L). Failure to account for this decline in testosterone concentrations in regularly cycling women before the menopause would result in inappropriate conclusions about the influence of menopause on T if average levels in older women are compared with those in younger women, particularly those less than 30 yr of age.

It should be noted that very limited previous studies (18) have indicated that a midcycle rise in total T concentrations occurs in regularly cycling women. Mushayandebvu *et al.* (18) reported that in older reproductive aged women, this midcycle T peak in free concentrations in particular is lost.

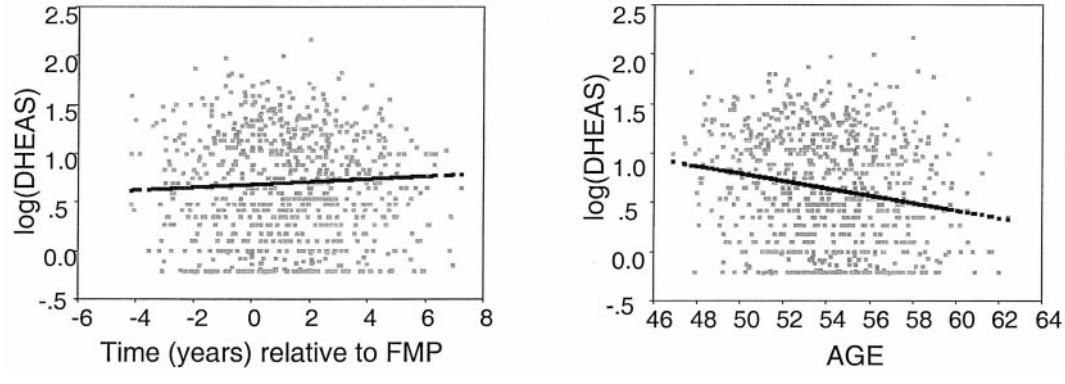

FIG. 5. Linear regression model: observed log(DHEAS) and fitted levels of mean log(DHEAS) across the menopausal transition (a) and *vs.* age (b). The *horizontal axis* in a represents time (years) with respect to FMP (0); negative (positive) numbers indicate time before (after) FMP. The fitted line in a is for median levels of age (53) and BMI (25), and that in b is for median levels of time (0) and BMI (25).

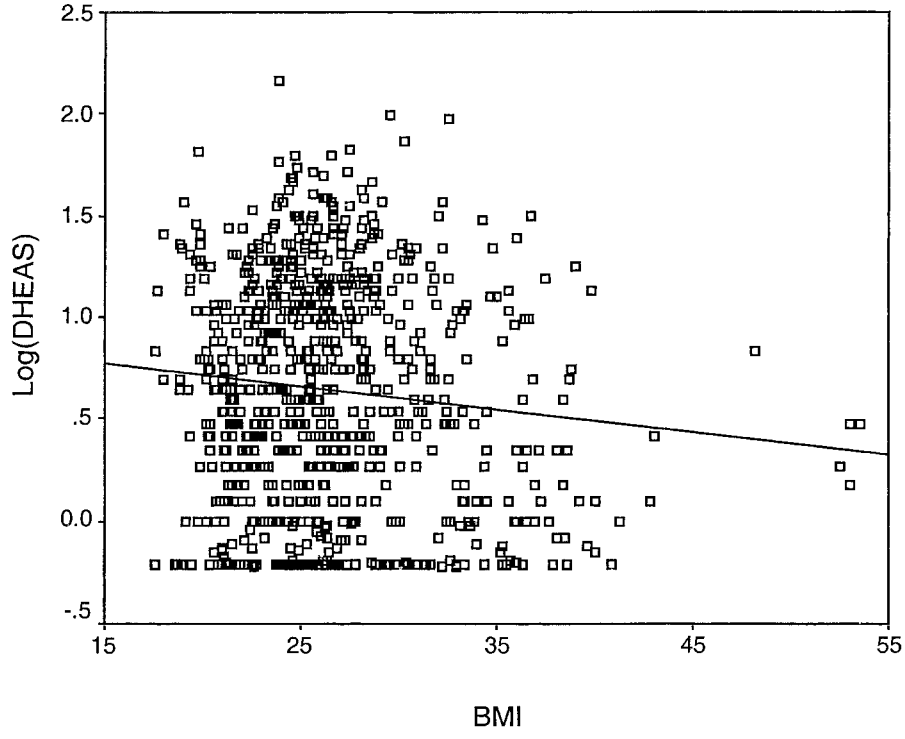

FIG. 6. Scatterplot of log(DHEAS) *vs.* BMI. r = −0.10; $P < 0.01$.

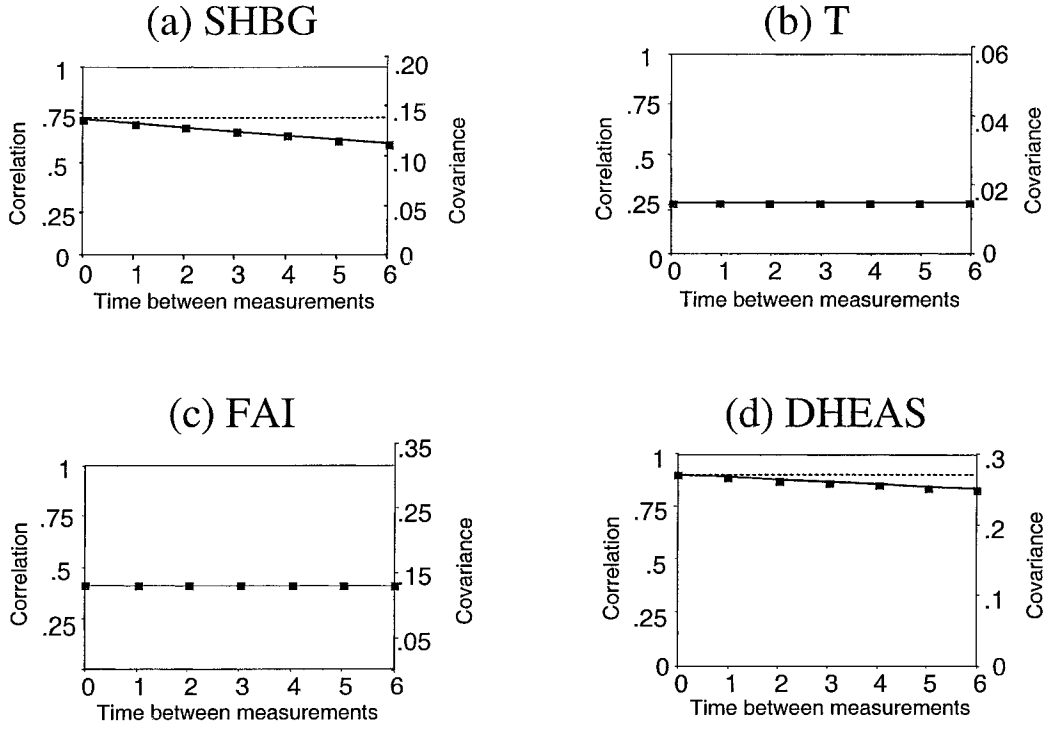

FIG. 7. Correlation between repeated measurements over time and corresponding covariance estimates for SHBG (a), T (b), FAI (c), and DHEAS (d).

This observation, however, would not account for our inability to demonstrate any change in T across a 12-yr period encompassing FMP.

The changes in SHBG are also controversial. Some previous studies (2, 19) have demonstrated a clear-cut fall in SHBG concentrations related to the menopause, *e.g.* a fall of approximately 15% in the data of Rannevik *et al.* (2). Bancroft and Cawood (3) showed no significant change in SHBG levels in comparing pre-, peri-, and postmenopausal women. Longcope *et al.* (20), on the other hand, reported an 81% increase in SHBG concentrations in a group of 241 women who were initially pre- or perimenopausal and who were

followed for a 3-yr period. Although their estrogen levels declined by 32–45%, there was a substantial increase in SHBG. The present report indicates an overall 43% decrease in SHBG from 4 yr before FMP to 2 yr thereafter. The time of maximum change was estimated to be 2 yr before FMP. The levels of SHBG were negatively associated with BMI and were positively correlated with log(E_2). About a third of the decline in mean SHBG levels was explicable by changes in E_2 and BMI. There is no obvious explanation for this very substantial difference in results.

The T to SHBG ratio was used to calculate FAI, which has been reported to be a reasonable index of free T concentrations in women (21). In light of the absence of any change in total T and a fall in SHBG, the FAI rose by 80% over 6 yr, from 1.5 at −4 yr to 2.7 at +2 yr. Again, the time of maximum change was approximately 2 yr before FMP. As expected, the FAI was positively associated with BMI, but was not related to age or E_2. This increase in FAI needs to be taken into account in any model in which it is proposed that a decline in sexual function associated with the menopause transition or menopause might be etiologically related to changes in free androgen levels.

With regard to DHEAS, a number of studies have demonstrated a progressive decline in its circulating concentrations as a function of age, starting in the mid teens or early twenties (7, 22). The decline is linear and shows no obvious relationship with ovarian function, although a previous study (8) had suggested that ovarian factors not related to E_2 might significantly influence this reduction in DHEAS levels independently of age. In the present study it was noted that mean DHEAS levels were not related to FMP, but did decrease significantly with age and with BMI. There was 1.5% decrease for each year of age and a 3.8% decrease for each unit increase in BMI. We saw no relationship with menopausal status.

Several previous studies used small sample sizes and were cross-sectional, or if longitudinal, the use of cross-sectional reduction in the statistical analysis impacted on the results obtained. Thus, this is the first prospective study of a population-based sample through the menopausal transition, which overcomes previous methodological problems of sample derivation, length of follow-up, accurate recording of date of FMP, use of an appropriate statistical technique to capture the repeated measurements, and control for the influence of confounding factors.

In summary, the present study, derived from a large prospective longitudinal cohort, failed to show any change in total T in relation to FMP. A clear-cut fall in SHBG with the associated rise in FAI was observed. There was a fall in DHEAS uninfluenced by the menstrual transition and menopause. It is clear that the interactions between androgens and estrogens across the menopausal transition and postmenopausally deserve further investigation in the pathogenesis of the symptoms related to the menopause and perhaps the pathogenesis of disorders that follow it, such as bone loss.

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