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Lower Serum DHEAS levels are associated with a higher degree of physical disability and depressive symptoms in middle-aged to older African American women

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Abstract

Background— Changes in androgen levels and associations with chronic disease, physical and neuropsychological function and disability in women over the middle to later years of life are not well understood and have not been extensively studied in African-American women.

Aims— The present cross-sectional analysis reports such levels and associations in community dwelling, African American women aged 49 – 65 years from St. Louis, Missouri.

Methods— A home-based physical examination and a health status questionnaire were administered to randomly sampled women. Body composition (DEXA), lower limb and hand-grip muscle strength, physical and neuropsychological function and disability levels were assessed. Blood was drawn and assayed for total testosterone (T), sex hormone-binding globulin (SHBG), dehydroepiandrosterone-sulfate (DHEAS), oestradiol (E2), adiponectin, leptin, triglycerides, glucose, C-reactive protein (CRP) and cytokine receptors (sIL2r, sIL6r, sTNFr1 & sTNFr2). Multiple linear regression modelling was used to identify the best predictors of testosterone, DHEAS and Free Androgen Index (T/SHBG).

Results— Seventy-four percent of women were menopausal and a quarter of these were taking oestrogen therapy. DHEAS and E2 declined between the ages of 49 and 65 years, whereas total T, SHBG and FAI remained stable. Total T and DHEAS levels were strongly correlated. In this population sample there were no independent associations of either total T or FAI with indicators of functional limitations, disability or clinically relevant depressive symptoms. Unlike total T and FAI, lower DHEAS levels was independently associated with both higher IADL scores (indicating a higher degree of physical disability) and higher CESD scores (indicating a higher degree of clinically relevant depressive symptoms).

Conclusion— There is an age-related decline in serum DHEAS in African-American women. Lower DHEAS levels appear to be associated with a higher degree of physical disability and depressive symptoms in this population.

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Introduction

Changes in androgen levels in women over the middle years of life are not well understood. It has been reported that, cross-sectionally, androgen levels in women decline rapidly with age during early reproductive years but do not change as a result of menopause because of continued androgen production by the ovary and adrenals [1,2]. Burger et al. (2000) reported a longitudinal decrease in DHEAS with age in women aged 45 – 55 years, an increase in SHBG and a decrease in FAI at the time of menopause, with no change in total T [3]. Androgen changes across the midlife have not been extensively studied or specifically reported in African-American women.

Associations between androgen levels, body composition, metabolic and inflammatory markers, and physical and neuropsychological function have not been well described in women during the midlife. Santoro et al. (2005) reported strong associations between androgens and physical characteristics (waist circumference and BMI) and the metabolic syndrome and weak associations with physical function, sexual desire and arousal and well-being in the Study of Women Across the Nation (SWAN) [4]. Some of these associations are somewhat modified by ethnicity (Santoro & Crawford, personal communication, March 2006) and deserve closer scrutiny. Barrett-Conner et al. reported that serum DHEAS level but not that of any other sex steroid was associated with depressed mood in older women [5].

The present study reports serum total T, DHEAS and FAI levels and describes the associations between hormones, body composition, adipokines and cytokine receptor levels, chronic disease, medication and function in a group of community dwelling, African-American women aged 49 – 65 years.

Materials and Methods

Population

The sampling and data collection procedures have been previously described in detail [6,7]. Briefly, data for this study are from the African-American Health (AAH) project, a population-based longitudinal study of 998 men and women aged 49 – 65 initiated to examine key issues of disability and frailty among African-Americans. Sampling was designed to recruit approximately equal proportions of participants from two socio-economically diverse strata. One group was from a poor, inner city area of St. Louis, MO and the other was from suburbs adjacent to the north and west of the city. Inclusion criteria were the following: a) self-reported Black or African-American race; b) birth year from 1936 to 1950, inclusive; c) Mini-Mental Status Examination (MMSE) score of 16 or greater; and d) willingness to provide written informed consent. Baseline evaluations were done between 2000 and 2001, and the response rate was 76%.

The sample population entered in the present analysis consisted of the subset of women (n=244/627; 39%) from the AAH project who donated blood at baseline. Participants (n=244) had a mean age of 56.9 ± 4.4 years (distribution: 49-54 yrs, N=92; 55-60 yrs, N=90; 61-65 yrs, N=62) and BMI of 31.9 ± 7.0 kg/m² (range 15.7-55.2). Responders [ie women who donated blood at baseline for nested special studies (n=244; BMI= 31.9 ± 7.0)] did not differ significantly (t-value = 0.51; p=0.61) from non-responders (n=383; BMI= 31.6 ± 7.9) on BMI. Therefore, the BMIs of women in this study were similar to all other women in the AAH study (i.e., a BMI of ~31 is characteristic of women in the AAH project). Within this sub-group of women, N=180 women were menopausal [n=70 natural + n=110 had hysterectomy] and N=64 were peri- or non-menopausal. This study was approved by the Saint Louis University Institutional Review Board (IRB).

Physical examination, interview and questionnaires

A home-based physical examination and a health status questionnaire were used to record co-morbid disease. The questionnaire included age, environmental characteristics (city or suburbs) and annual income. Chronic conditions were assessed by asking the participant whether “their doctor ever told them they have” hypertension, diabetes, cardiovascular disease (angina, heart failure or heart disease) or stroke. All medications, prescription and over-the-counter, were recorded by the interviewer during the in-home assessment. Medications were categorized as oral anti-diabetic, anti-hyperlipidemic, anti-hypertension (further classified as angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, anti-adrenergic, beta-blocker, calcium channel blocker and diuretic), oestrogen (hormonal replacement therapy (HRT)) and thyroxine. Present smoking was obtained by direct inquiry.

Hip circumference was determined using a tape measure at the level of the maximum posterior protrusion of the buttocks. Waist circumference was measured one centimeter above the iliac crests. Waist-to-hip ratio (WHR) was calculated. Body mass index (BMI) was calculated based on measured height and weight (kg/m^2).

Body composition—Total body lean mass (LM) and fat mass (FM), the composition of the appendicular skeletal mass (ASM) and bone mineral density of cervical spine, hip and lumbar spine were evaluated by dual-energy x-ray absorptiometry (DEXA [Hologic QDR 4500 W]).

Muscle strength and physical function—Isokinetic strength testing of lower limbs (flexion and extension at ankle, knee and hip) was performed using Biodex System 3 Pro (Biodex Medical Systems; Shirley, NY). Peak torque, work, power, time-to-peak torque and the angle of the joint at which peak torque was obtained were assessed through 60-degrees and 120-degrees of motion. Data were corrected for body weight. Only peak torque data generated through 120-degrees of motion were used in these analyses.

Isometric grip strength was assessed using a handgrip dynamometer (Jamar, Jackson, MI). The mean of three maximal effort trials with the self-reported strongest hand was used in these analyses. Participants completed the test seated in a chair (without arm rests) with feet flat on floor while holding arm flat against side with elbow at 90 degrees.

The sit-stand test measured the time taken to accomplish five complete raises from a chair. The gait speed test measured the average time (2 trials) taken to walk a 4-meter course at a usual pace, as if walking to the store. The 6-minute walk test measured the distance (meters) walked in the allotted 6 minute time period on a ninety-foot pathway.

Activities of daily living (ADL's) were assessed [8]. These consisted of seven basic ADL's (BADL's; having any difficulty with bathing, dressing, eating, getting in to and out of bed or chairs, walking across a room, getting outside, and using the toilet; potential range 0 – 7 [mean $\pm$ S.D. for this study was 0.93 ± 1.67]) and eight instrumental ADL's (IADL's; having any difficulty with preparing meals, shopping for groceries, managing money, making phone calls, doing light housework, doing heavy housework, getting to places outside of walking distance, and managing medications; potential range 0 – 8 [Mean $\pm$ S.D. 1.07 ± 1.73]). Functional limitations (Nagi scores) [9] were assessed for lower body (difficulties in walking a quarter of a mile, walking up and down 10 steps without rest, standing for 2 hours, stooping, lifting 10 pounds, and pushing large objects; range 0 – 6 [Mean $\pm$ S.D. 2.02 ± 1.87]) and upper body (difficulties reaching up over one's head, reaching out as if to shake hands, or grasping; range 0 – 3 [Mean $\pm$ S.D. 0.656 ± 1.033]). Physical activity levels were assessed by using the Yale Physical Activity Study (YPAS) scale [10].

Neuropsychological function—The MMSE is a tool used to detect cognitive deficits seen in syndromes of dementia and delirium and for measuring these cognitive changes over time [11]. A score of 23 or below is 87% sensitive and 82% specific in detecting dementia and delirium when a psychiatrist's standardized clinical diagnosis is used as the criterion [12]. Depressive symptoms were assessed by the 11-item Center for Epidemiologic Studies Depression Scale (CESD). A score of 9 or more was used as an indicator of a clinically relevant level of depressive symptoms; a score of 9 on the abbreviated scale is equivalent to the standard criterion of 16 or more on the original 20-item version [6,13]. The prevalence of clinically relevant depressive symptoms in this study was 25% (N=61/244).

The trail-making test (TMT) is a test of visuomotor tracking and attention [14]. Crowe et al. (1998) demonstrated that performance on Part A of the trail making test was uniquely determined by visual search and motor speed and that performance on part B was determined by lowered reading level, poor skill in visual search, poor ability to maintain two simultaneous sequences and decreased attention and working memory functions [15]. Part A of the test consists of circled numbers 1-25 on a page. Participants were first given a sample trail to ensure they understood the task. They traced a line beginning at circle 1 and ending at circle 25 in as little time as possible. If errors were made they were immediately asked to restart from the last correct move. Part B of the test consists of numbers 1-13 and letters A-L on a page. Participants were required to draw a specific trail between these circles alternating sequentially between numbers and letters in as little time as possible. The trail making tests are reported as the ratio of part B:part A (TMT-B:TMT-A), an index of executive function [16], lower scores indicate better executive function.

Laboratory Analyses

Blood was drawn for laboratory analyses at the time of the DEXA examination. Thus, blood chemistry variables represent neither fasting nor morning values. Adiponectin was determined using a commercially available RIA kit (Linco Research, St. Charles, MO, USA). In this laboratory, intra- and inter-assay coefficients of variation (CVs) were 5.3% and 8.1% respectively. Serum E2 and leptin were measured using an RIA kit (Diagnostic Systems Laboratories, Santa Monica, CA, USA). The intra- and inter-assay CVs were 6.5% and 9.7% for oestradiol and 4.7% and 5% for leptin. Serum DHEAS was measured using an RIA kit (Diagnostic Products Corp). The intra- and inter-assay CV's were 5.3% and 7.0% respectively. Total T was measured using an RIA kit (ICN-Biomedicals) with intra- and inter-assay CVs of 6.7% and 7.3%. SHBG was determined using an RIA kit (Diagnostics Systems Lab Inc) with intra- and inter-assay CVs of 3.7% and 10.2%. The FAI, was calculated as T/SHBG. Triglycerides were measured using a commercially available enzymatic kit from Roche Diagnostics (Indianapolis, IN). In this laboratory, triglycerides had an intra-assay CV of 1.1% and an inter-assay CV of 3.6%. Serum glucose measurement was performed in a commercial clinical laboratory (Smith Kline-Beecham, St. Louis, MO). CRP was measured with a commercially available High Sensitivity Enzyme Immunoassay (hsCRP ELISA) kit from MP Biomedicals (Orangeburg, NY). The intra-assay and inter-assay CV's were 4.5% and 4.1% respectively. Soluble IL2r was measured using an ELISA kit (PIERCE, Rockford, IL), intra- and inter-assay CV's were 10%. Soluble IL6r was measured with an ELISA kit from ICN-Biomedicals. (Costa Mesa, CA). The intra- and inter-assay CV's were 5.0% and 5.9%. Soluble TNFr1 and sTNFr2 were measured using an ELISA kits (BioSource, Camarillo, CA). Intra- and inter-assay CV's were 4.1% and 7.3% for sTNFr1 and 5.1% and 8.6% for sTNFr2.

Statistical Analysis

Most hormonal variables presented a log normal distribution. Testosterone, adiponectin, leptin, SHBG, DHEAS, FAI, E2, triglycerides, CRP and soluble interleukin (IL) and tumour necrosis

factor (TNF) receptors (sIL2r, sIL6r, sTNFr1 & sTNFr2) were normalized by transformation into their natural logarithm.

Linear regression (continuous variables) in combination with correlation analyses, one-way analysis of variance (ANOVA, ordered variables) or independent samples t-tests (dichotomous variables) were used in the whole population to detect potential predictors of testosterone, DHEAS and FAI. Variables significantly associated with androgen levels at an alpha level of 0.05 were further included together in multiple regression predictive models in the whole sample. Because of the high number of variables passing the statistical cut-off for inclusion in multivariate models and the co-linearity between many of these, an intermediary multiple regression step was performed within variable class (i.e. blood chemistry, physical function, body composition (muscle & fat), bone mineral density (BMD), chronic health conditions and medication). Where all variables in a class displayed co-linearity the most relevant or most significant factor was chosen for inclusion in the final models (for an example using Total T modelling see, Figure 1).

Multiple regression data were presented as the predictive value of the model (adjusted-R²) and associated P-value. The impact of individual factors was expressed as β coefficients and associated P-values. Data analyses were performed using Intercooled Stata 7.0 (STATA Corporation, College Station, TX). Figures were generated using GraphPad Prism 4.0 (GraphPad Software Inc. San Diego, CA).

Results

Strata, age & hormones

Sample characteristics, by geographic strata are shown in Table 1. Hormone levels and age of participants were not statistically different between the inner city and suburban strata. There was a vastly greater proportion of inner city women living in households with an annual income of less than \$20,000 when compared to their suburban counterparts (58.9% compared with 26.6%). An analysis of sample characteristics, by menopausal status revealed that menopausal women were older (57.9 ± 4.3 compared with 54.2 ± 3.5 years; $P < 0.0001$) and had lower total T (12.03 ± 11.27 compared with 15.51 ± 13.19 ng/dL, $P = 0.047$) and higher SHBG levels (50.76 ± 30.70 compared with 41.57 ± 24.04 nmol/L, $P = 0.035$) when compared with peri- or non-menopausal women. There was no significant difference in DHEAS or E2 levels between menopausal and peri- or non-menopausal women. This was likely due to the prevalence of estrogen replacement therapy in this group ($N = 48/180$, 26.7%).

In the whole group of women, DHEAS ($P = 0.011$) and E2 ($P = 0.032$) declined over the 15-year age span but total T, SHBG and FAI did not (Table 2). By definition total T and FAI were strongly positively correlated. DHEAS levels were positively associated with total T, FAI and E2 levels and inversely associated with SHBG levels (Table 2). Table 2 also describes the mediation effect of menopausal status on associations between the hormonal variables. The major difference between menopausal and non-menopausal women was that E2 levels were positively associated with SHBG levels. This also drove an inverse association between E2 levels and FAI.

Associations with total testosterone

Blood chemistry—Total T levels were positively associated with CRP ($P = 0.01$) and inversely associated with adiponectin ($P = 0.0003$) (Table 3). No other biochemical measures were associated with total T levels.

Muscle strength and physical function—Higher total T levels were associated with lower peak torque corrected for body weight of the knee extensors measured through 120-degrees of motion ($P = 0.031$, Table 3). Higher total T was associated with faster 6-meter walk time ($P = 0.027$) but with shorter 6-minute walk distance ($P = 0.016$, Table 3).

Body composition—Higher total T levels were associated with higher BMI ($P = 0.003$), waist circumference ($P = 0.01$), total ASM ($P = 0.0007$) and inversely associated with the percent of lean mass in the appendicular skeleton ($P = 0.041$) (Table 3). Both fat and lean masses, corrected for body height, were positively associated with total T ($P = 0.0005$ & 0.0007 , respectively, Table 3). Total T was positively associated with BMD of the cervical spine ($P = 0.002$), trochanter ($P = 0.004$), intertrochanter ($P = 0.006$), total hip ($P = 0.002$) and lumbar spine ($P = 0.004$) (Table 3).

Neuropsychological function—Total T was not associated with any measure of neuropsychological function.

Chronic health conditions & medications—Total T levels were not significantly different in women with any of the assessed health conditions ($P > 0.05$). However, women taking hormone medication [general] ($t=2.85$, $P=0.0047$), estrogen [specifically] ($t=4.47$, $P<0.0001$) and beta-blockers ($t=2.1$, $P=0.037$) all had lower serum T levels than women not taking these classes of medications (data not shown).

Multivariate modelling of total T—Intermediate multiple regression analysis within variable class (see Figure 1) showed that DHEAS and SHBG were associated with total T ($P < 0.05$), independent of CRP and adiponectin. Peak torque, corrected for body weight of the knee extensor muscles through 120-degrees of motion and gait speed were inter-related and the peak torque variable was selected for inclusion in the final model. All body composition (muscle and fat) variables were highly inter-related and total body lean mass, corrected for height was selected for inclusion in the final model. BMD at all sites was highly inter-related; total hip BMD was included in the final model. Oestrogen and beta-blocker medications were included in the final model and hormone medications (general) was dropped as it was a parent variable to oestrogen. The final model (Table 4) significantly predicted 38% of the variation in serum total T levels in the cohort ($P < 0.0001$). The most important factor accounting for close to half of the predictive value of the model was DHEAS (when removed, R^2 dropped to 0.23) and the second most important factor was log SHBG (when removed with DHEAS, R^2 dropped to 0.13).

Associations with FAI

Blood chemistry—FAI was positively associated with CRP ($P = 0.001$), glucose ($P = 0.035$), triglycerides ($P = 0.042$), leptin ($P = 0.034$) and negatively associated with adiponectin ($P < 0.0001$) (Table 3).

Muscle strength and physical function—FAI was inversely associated with peak torque, corrected for body weight, of ankle and knee extensors measured through 120-degrees of motion ($P = 0.018$ & 0.015 , respectively) and also with distance walked during the 6-minute walk test ($P = 0.013$) (Table 3).

Body composition—FAI was positively associated with BMI ($P = 0.0001$), waist circumference ($P = 0.002$), total ASM ($P = 0.0001$) and inversely associated with the percentage of lean mass in the appendicular skeleton ($P = 0.018$) (Table 3). Both fat and lean mass corrected for height ($P < 0.0001$ & $= 0.0001$, respectively) were positively associated with FAI (Table 3). Greater BMD in the cervical spine ($P = 0.0007$), trochanter ($P = 0.001$), intertrochanter (P

= 0.003), total hip ($P = 0.001$) and lumbar spine ($P = 0.002$) were also associated with higher FAI (Table 3).

Neuropsychological function—FAI was not associated with any measure of neuropsychological function.

Chronic health conditions & medications—FAI was not different in women with any of the assessed health conditions (P 's > 0.05). However, women taking anti-diabetic medication ($t=2.31$, $P=0.022$), hormone medication [general] ($t=4.18$, $P<0.0001$), estrogen [specifically] ($t=6.63$, $P<0.0001$) and beta-blockers ($t=1.97$, $P<0.05$) all had lower serum FAI's than women not taking these classes of medications (data not shown).

Multivariate modelling of FAI—Intermediate multiple regression analysis within variable class showed that DHEAS and adiponectin were associated with FAI, independent of CRP, glucose, triglycerides and leptin (P 's < 0.05). Peak torque, corrected for body weight of the knee and ankle extensor muscles through 120-degrees of motion and 6-minute walk distance were inter-related and the two peak torque variables were selected for inclusion in the final model. As was the case with the total T modelling, all body composition (muscle and fat) and BMD variables were highly inter-related within class and total body lean mass, corrected for height and total hip BMD were included in the final model. Oestrogen and beta-blocker medications were included in the final model, hormone medications (general) was dropped as it was a parent variable to oestrogen. Anti-diabetic medication was dropped due to inter-relatedness with other medications. The final model (Table 5) significantly predicted 42% of the variation in serum FAI levels in the cohort ($P < 0.0001$). As with the total T model, the most important factor accounting for close to half of the predictive value of the model was DHEAS (when removed, R^2 dropped to 0.24, and lean mass/height reached significance, $P = 0.041$). Taking oestrogen medication was the second most important factor (when removed with DHEAS, R^2 dropped to 0.15) predictive of lower FAI. Higher log adiponectin was also an important independent predictor of lower FAI.

Associations with DHEAS

Blood chemistry—DHEAS was positively associated with CRP ($P = 0.0001$) and inversely associated with adiponectin ($P = 0.001$), sTNFr1 and sTNFr2 ($P = 0.007$ & < 0.0001 , respectively) (Table 3).

Muscle strength and physical function—DHEAS was not associated with body weight corrected peak torque generation in flexor or extensor muscle groups of the ankle, knee or hip through 120-degrees of motion. DHEAS was inversely associated with IADL scores ($P = 0.041$) (Table 3).

Body composition—Higher DHEAS levels were associated with higher BMI ($P = 0.004$) and higher waist circumference ($P = 0.035$) (Table 3). DHEAS was positively associated with both total body fat and lean mass, corrected for height ($P = 0.021$ & 0.009 , respectively) and with total ASM ($P = 0.016$), but not with the percent of lean mass in the appendicular skeleton (Table 3). Higher DHEAS was associated with greater BMD of the cervical spine ($P = 0.036$), trochanter (0.046), intertrochanter ($P = 0.014$), total hip ($P = 0.017$) and lumbar spine ($P = 0.008$) (Table 3).

Neuropsychological function—DHEAS was inversely associated with scores on the CESD ($P = 0.018$), but not with any other measure of neuropsychological function (Table 3).

Chronic health conditions & medications—DHEAS levels were significantly lower in women with CHD ($t=2.81$, $P=0.0053$) and CHF ($t=3.58$, $P=0.0004$). Women taking oestrogen ($t=1.97$, $P<0.05$) and beta-blockers ($t=2.53$, $P=0.012$) had significantly lower serum DHEAS levels and women taking calcium channel blockers had significantly higher serum DHEAS levels than women not taking these classes of medications ($t=-2.62$, $P=0.009$, data not shown).

Multivariate modelling of DHEAS—Intermediate multiple regression analysis within variable class showed that total T, CRP and sTNFr2 were associated with DHEAS, independent of other blood chemistry variables. As stated previously, all body composition (muscle and fat) and BMD variables were highly inter-related within class and total body lean mass, corrected for height and total hip BMD were included in the final model. Beta-blocker and calcium-channel blocker medications were included in the final model. Oestrogen medications, CHF and CHD were dropped due to inter-relatedness with beta-blocker and calcium-channel blocker medications. The final model (Table 6) significantly predicted 38% of the variation in serum DHEAS levels in the cohort ($P < 0.0001$). The most important factor accounting for close to half of the predictive value of the model was total T (when removed, R^2 dropped to 0.22). Taking calcium-channel blockers was an important independent predictor of higher DHEAS levels. From a functional perspective, lower IADL and CESD scores were important independent predictors of higher DHEAS levels.

Associations with Oestradiol (E2)—Serum E2 declined significantly with age (Table 2). In bivariate regression analyses, higher serum E2 levels were associated with lower adiponectin ($\beta = -0.16$, $P = 0.001$) and sTNFr1 levels ($\beta = -0.09$, $P = 0.02$), and higher leptin ($\beta = 9.30$, $P = 0.001$), SHBG ($\beta = 0.11$, $P = 0.014$) and DHEAS levels ($\beta = 0.15$, $P = 0.011$). Higher E2 was also associated with higher BMI ($\beta = 1.40$, $P = 0.008$), better performance on the sit-stand ($\beta = -0.71$, $P = 0.018$) and knee extension peak torque tests ($\beta = 2.95$, $P = 0.012$), and with better MMSE ($\beta = 0.38$, $P = 0.042$) and CESD scores ($\beta = -0.09$, $P = 0.0048$). Diabetic women and women taking anti-diabetic medications had lower serum E2 levels ($P = 0.014$ & 0.024 , respectively). Not surprisingly women taking oestrogen replacement therapy had higher serum E2 levels than women not taking oestrogen ($P < 0.0001$).

A multivariate regression model including the above factors predicted 23% of the variance in serum E2 levels ($P = 0.0014$). Oestrogen replacement therapy ($\beta = 0.684$, $P = 0.012$), leptin ($\beta = 0.008$, $P = 0.023$) and SHBG ($\beta = 0.375$, $P = 0.035$) were the significant individual factors in the model.

Discussion

The present study shows a significant cross-sectional decline in serum DHEAS and E2 levels and stable testosterone, SHBG and, consequently, FAI levels in African-American women from 49 to 65 years of age. The findings may not reflect the natural behaviour of hormones across this age range as 48 women from the sample of 244 were using exogenous oestrogen. Adrenal androgens have been demonstrated to decline by approximately 80% over the adult female lifespan [17,18]. Burger et al. (2000) reported, in 172 women, that DHEAS declined with aging and was not related to final menstrual period [3]. These authors also noted that SHBG and FAI changed at the menopause, partially as a result of the decline in E2 production, and that total T was stable over the menopausal years [19].

The present study highlights the strong relation between serum DHEAS and testosterone production in adult women. DHEAS is primarily secreted by the adrenal glands and is the precursor hormone for the synthesis of testosterone. Testosterone production is also strongly related to circulating SHBG concentrations. SHBG not only acts to transport and buffer the biological effects of steroid hormones (including testosterone and oestrogen), by limiting it's

transport in to cells, but also interacts in various tissues with the membrane bound SHBG receptor (SHBG-R) and a consequent steroid ligand to initiate intracellular signaling via adenylate cyclase and cyclic AMP [20]. It is likely that this signaling cascade cross-talks with the classical intra-cellular androgen receptor (AR) to elicit genomic transcriptional events [20]. These cellular processes may also be involved in a complex feedback mechanism with the hypothalamic-pituitary-adrenal and -ovarian axes (and testicular in men) to regulate the production of androgens, and consequently with the liver to regulate SHBG production, thereby maintaining the appropriate partitioning between circulating free and bound hormone.

Total T and FAI, an index of the fraction of testosterone in the circulation that is not bound to SHBG, were significantly lower in women who were taking oestrogen replacement therapy. It is likely that the effect of oestrogen replacement on FAI was due to both a decrease in secreted testosterone and an increase in circulating SHBG levels. The positive association between E2 and SHBG in the present cohort further evidences this. Transdermal estrogen replacement therapy has been shown to increase SHBG and decrease androstenedione levels, without altering the levels of total T, DHEA or DHEAS [21].

In the present study, serum adiponectin levels were inversely associated with total T, FAI DHEAS and E2 levels in bivariate analysis, but only remained a significant predictor in the multivariate models of FAI. Thus, it is likely that the major association occurs through a relation with SHBG. However, testosterone has been reported to decrease the level of the high molecular weight complex of adiponectin in the circulation, the form that is reportedly found in higher concentrations in females when compared with males [22]. Low levels of SHBG have been linked to higher rates of diabetes [23] and cardiovascular disease events [24]. Potential mechanisms to explain these associations might be a direct effect of SHBG on lipid metabolism or SHBG might be a marker of insulin resistance as insulin has a direct inhibitory effect on SHBG. Low levels of SHBG may, at least in part, be a risk factor contributing to the higher incidence of diabetes and cardiovascular disease through a decreasing level of adiponectin. Obese subjects usually have a lower level of adiponectin and lower level of SHBG when compared to non-obese subjects [25].

The present study indicates a positive independent association between calcium-channel blocker use and serum DHEAS level. It has been reported that the calcium-channel blockers, amlodipine [26,27], manidipine and cilnidipine [28] raise serum DHEA and DHEAS levels in insulin resistant obese and hypertensive men and women, but nifedipine does not [29]. Moreover, DHEAS is an endogenous activator of the peroxisome-proliferation pathway of fatty acid beta-oxidation and calcium-channel blockers have been shown, by reducing the expression of CYP4A and acyl-CoA oxidase mRNA, to inhibit this effect [30,31], at least in cultured hepatocytes.

The results from the present study indicate that higher DHEAS levels are associated with better physical function status, in terms of lower IADL scores and less depressive symptomology, as indicated by lower CESD scores. These results are in agreement with those of Santoro et al. (2005) who reported a positive association of DHEAS with self-reported health and functional status, as measured by the functional domain of the SF-36, and an inverse association of DHEAS with CESD scores [4]. However, after adjustment for ethnicity, site, age, smoking and log waist circumference, the association with CESD scores was no longer significant. These authors did, however, report a significant inverse association between FAI and CESD scores after adjustment for the aforementioned factors [4]. Although there was a trend towards an inverse association between FAI and CESD scores in bivariate analysis, the present study failed to identify an independent association between the two variables in multivariate analysis. The population of the SWAN study [4] differs fundamentally from the population of the present study in a number of ways. Firstly, ethnically and geographically: the SWAN study is a multi-

ethnic (Caucasian, African-American, Hispanic, Chinese-American & Japanese-American), multi-site (Detroit, Boston, Chicago, Pittsburg, Newark, Oakland & Los Angeles) study, whereas the present study recruited solely African-American participants from two geographical areas within St. Louis. Secondly and perhaps more importantly, SWAN participants were regularly cycling women in the early stages of the menopause (ages 40–55 years), whereas AAH participants were aged 49–65 years and predominantly postmenopausal (approx. 74%), over a quarter of whom were taking exogenous oestrogen. It is possible, that although androgens of both adrenal and ovarian origin do not change markedly across the menopausal transition [19], differences in associations with functional outcomes may be evident.

Androgen supplementation in healthy premenopausal and postmenopausal women with androgen insufficiency is controversial. In fact, to date, no formal definition of female androgen insufficiency based on strong empirical data exists [32]. However, reduced mood, well-being and libido, have been reported to respond well to testosterone replacement [32,33]. Data on DHEA supplementation in peri- and post-menopausal women is limited to a small number of well-designed randomized-controlled trials (RCT) most of which show little or no benefit on symptoms over that of placebo (for a comprehensive review of androgen therapy in women see Arlt (2006)[33]). A RCT of DHEA in peri-menopausal women with complaints of mood and well-being showed no improvement in symptoms when compared to placebo[34]. Another, in post-menopausal women with fibromyalgia showed no improvement in quality of life, cognitive function, mood, pain, fatigue or functional impairment [35].

A major discrepancy between the present study and those of others [4,19] was the positive rather than inverse association between DHEAS and indices of body morphometry (BMI and waist circumference). The present study also showed positive associations of DHEAS with other body composition variables determined by DEXA; height corrected total body fat and lean mass and total ASM. These associations were also present with total T and FAI. Interestingly, there was an inverse association of total T and FAI with the percentage of lean tissue in the appendicular skeleton, but this was not significant for DHEAS. Again, it is possible that these discrepancies reflect differences in age and menstrual status of the populations. Also, Santoro et al. (2005) and Burger et al. (2000) sampled blood between menstrual cycle days 2 and 7 and days 4 and 8, respectively in cycling women, and 3 months after amenorrhea (median age 54 years) [19], whereas timing of blood sampling in the present study of predominantly noncycling women was based on convenience. Thus differences in timing of sampling may reflect pulsatile, diurnal and/or circannual rhythm differences in circulating DHEAS, T and SHBG levels. The median DHEAS level in the present study was 62 µg/dL (interquartile range = 55, 95% CI 15–95) compared with 114 µg/dL (interquartile range = 93.6)[4] and 1.9 µmol/L (70.5 µg/dL) (interquartile range = 2.65 (98.3 ug/dL), 95% CI 0.8–4.5 (29.7–167 µg/dL), DHEAS MW = 371)[19]. Similar differences were seen in total T and FAI levels between studies, although SHBG levels were similar. It is also possible that these discrepancies reflect differences in DHEAS levels and associations with body composition in African-American compared to Caucasians and women of other ethnicities. In fact, in the SWAN study, African-American women did have significantly lower DHEAS levels than Caucasian women (88.75 (95% CI 84.94–92.74) v 115.58 (95% CI 111.82–119.48), $P < 0.0001$). Moreover, there is an excess of frank and subclinical disability in the present cohort [7] and many households are severely disadvantaged socially and economically and this may account, at least in part, for differences in androgen levels and modification of associations with body composition and function. Local androgen metabolism likely plays a major role in tissue-specific biological effects of androgens.

This study concludes that in African-American women, serum DHEAS and E2 levels decline cross-sectionally between the ages of 49 and 65 years, whereas total T, SHBG and FAI remain

stable, however this conclusion is limited by use of exogenous oestrogen in 20% of this sample. In terms of function, DHEAS but not total T, FAI or E2 was independently, inversely associated with scores on both physical disability (IADL score) and neuropsychological function (CESD score) assessment tools. This indicates that the age-associated decline in DHEAS may be either a cause or effect, at least in part, of a greater degree of physical disability and clinically relevant depressive symptoms in middle-aged to older African-American women.

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Figure 1.

The statistical modelling process using log total testosterone (T) as an example. The progression of potential predictor variables through bivariate, intermediate multivariate analysis within variable class and final multivariate analysis was identical for FAI and DHEAS modelling. Variables had to pass significance ($P < 0.05$) to progress from bivariate to intermediate multivariate analysis.

Table 1

Characteristics of the cohort of African American women recruited from randomly selected households in inner city and suburban St. Louis, Missouri, USA. Inner city dwelling women were more than twice as likely to live in households where the annual income was <\$20K. There were no significant differences in age, blood pressure, BMI, waist circumference or serum hormone levels between inner city and suburban dwelling women

		Mean	S.D.	Min.	Max.	N
Inner city	Age (years)	56.51	4.45	49	65	108
	Education (years)	12.54	2.97	1	25	107
	Annual Income <20K (%) ^a	58.9*				107
	SBP (mmHg)	136.85	31.31	70	229	108
	DBP (mmHg)	82.33	14.65	51	120	108
	BMI (kg/m ²)	32.22	6.96	16.31	55.27	107
	Waist (cm)	110.26	16.72	66.75	141.8	55
	Total T (ng/dL)	14.01	12.92	1	74	107
	SHBG (nmol/L)	45.94	24.93	11	128	107
	FAI (T _(nmol/L) /SHBG)	0.016	0.018	0.0003	0.102	107
	DHEAS (ug/dL)	70.68	44.89	3	217	108
	E2 (pg/mL)	17.32	15.48	2	87	108
Suburbs	Age (years)	57.21	4.41	50	65	136
	Education (years)	12.92	2.82	1	25	136
	Annual Income <20K (%) ^a	26.6*				128
	SBP (mmHg)	138.75	22.89	76	214	136
	DBP (mmHg)	80.77	11.91	45	137	136
	BMI (kg/m ²)	31.57	7.01	15.67	52.71	133
	Waist (cm)	109.71	17.23	76.75	146.4	64
	Total T (ng/dL)	12.04	10.89	1	76	133
	SHBG (nmol/L)	50.59	32.4	13	176	133
	FAI (T _(nmol/L) /SHBG)	0.014	0.016	0.0003	0.094	133
	DHEAS (ug/dL)	70.24	47.47	1	336	136
	E2 (pg/mL)	22.33	22.79	1	112	135

SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; T = testosterone; SHBG = sex hormone-binding globulin; FAI = free androgen index; DHEAS = dehydroepiandrosterone sulfate; E2 = oestradiol.

^a Annual household income has been reported as a categorical variable (i.e., % ≤ 20K for city and for suburbs).

Table 2

Associations between total testosterone (T), oestradiol (E2), dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG) and free androgen index (FAI). All data were analysed as log transformed data and are presented as Pearson correlation coefficients (R) and the number of observations (n) in parentheses

All Women						
	Age	Total T	SHBG	FAI	DHEAS	E2
Age						
Total T	-0.069 (240)	-0.069 (240)	-0.038 (240)	-0.067 (240)	-0.163 (244)	-0.138 (243)
SHBG	-0.038 (240)	-0.423 (240)	-0.423 (240)	0.923 (240)	0.493 (240)	0.087 (239)
FAI	-0.067 (240)	0.923 (240)	-0.741 (240)	-0.741 (240)	-0.260 (240)	0.159 (239)
DHEAS	-0.163 (244)	0.493 (240)	-0.741 (240)	0.476 (240)	0.476 (240)	0.163 (243)
E2	-0.138 (243)	0.087 (239)	0.159 (239)	-0.004 (239)	0.163 (243)	
Non-Menopausal (=Non- or Peri-menopausal)						
	Age	Total T	SHBG	FAI	DHEAS	E2
Age						
Total T	-0.008 (61)	-0.008 (61)	-0.033 (61)	-0.015 (61)	-0.237 (64)	-0.189 (63)
SHBG	-0.033 (61)	-0.38 (61)	-0.38 (61)	0.903 (61)	0.543 (61)	0.179 (60)
FAI	-0.015 (61)	0.903 (61)	-0.532 (61)	-0.532 (61)	-0.414 (61)	0.183 (60)
DHEAS	-0.237 (64)	0.543 (61)	-0.532 (61)	0.607 (61)	0.607 (61)	0.085 (60)
E2	-0.189 (63)	0.179 (60)	0.183 (60)	0.085 (60)	0.058 (63)	
Menopausal (=Yes or Hysterectomy)						
	Age	Total T	SHBG	FAI	DHEAS	E2
Age						
Total T	0.048 (179)	0.048 (179)	0.006 (179)	0.052 (179)	-0.111 (180)	-0.146 (180)
SHBG	0.006 (179)	-0.286 (179)	-0.286 (179)	0.808 (179)	0.346 (179)	-0.102 (179)
FAI	0.052 (179)	0.808 (179)	-0.546 (179)	-0.546 (179)	-0.213 (179)	0.494 (179)
DHEAS	-0.111 (180)	0.346 (179)	-0.213 (179)	0.390 (179)	0.390 (179)	-0.160 (179)
E2	-0.146 (180)	-0.102 (179)	0.494 (179)	-0.160 (179)	-0.066 (180)	

* P < 0.05,

** P < 0.01.

Table 3

Associations of log total testosterone (T), log free androgen index (FAI) and log dehydroepiandrosterone sulfate (DHEAS) with biochemical, physical and neuropsychological variables. Data presented are Pearson correlation coefficients (R) and associated P-values from linear regression analysis

	Log T		Log FAI		Log DHEAS	
	R	P-value	R	P-value	R	P-value
Biochemical						
Log CRP	0.166	0.01	0.21	0.001	0.24	0.0001
Log adiponectin	-0.23	0.0003	-0.30	<0.0001	-0.208	0.001
Log triglycerides	0.067	0.30	0.13	0.042	-0.067	0.301
Leptin	0.07	0.25	0.14	0.031	0.026	0.686
Log sIL2r	0.065	0.314	0.02	0.778	-0.047	0.469
Log sIL6r	0.005	0.937	-0.004	0.947	0.028	0.667
Log sTNF α 1	0.11	0.084	0.07	0.289	-0.175	0.007
Log sTNF α 2	0.06	0.349	0.01	0.843	-0.28	<0.0001
Glucose	0.05	0.44	0.14	0.035	0.037	0.58
Physical						
Systolic BP	0.06	0.334	0.03	0.646	-0.01	0.882
Diastolic BP	0.125	0.053	0.09	0.149	0.09	0.153
BMI	0.19	0.003	0.25	0.0001	0.188	0.004
Waist circumference	0.238	0.01	0.28	0.002	0.19	0.035
Max. grip strength	-0.002	0.979	0.03	0.622	0.013	0.851
BADL's	-0.006	0.927	-0.019	0.772	-0.05	0.395
IADL's	-0.021	0.75	-0.026	0.692	-0.13	0.041
Nagi upper body	0.036	0.583	0.016	0.807	-0.05	0.439
Nagi lower body	0.06	0.359	0.046	0.476	-0.11	0.081
YPAS	-0.11	0.083	-0.095	0.141	-0.06	0.314
Sit-stand test	0.08	0.451	0.11	0.284	-0.10	0.338
6 meter walk time	-0.235	0.027	-0.17	0.106	-0.12	0.25
6 minute walk distance	-0.256	0.016	-0.26	0.013	-0.048	0.652
Peak torque/body weight (120°)						
ankle extensors	-0.18	0.062	-0.23	0.018	-0.08	0.487
ankle flexors	-0.069	0.484	-0.11	0.264	0.002	0.986
knee extensors	-0.21	0.031	-0.238	0.015	0.02	0.813
knee flexors	-0.17	0.079	-0.155	0.144	-0.015	0.876
hip extensors	-0.10	0.335	-0.129	0.214	0.11	0.28
hip flexors	-0.147	0.155	-0.169	0.101	-0.08	0.442
Total skeletal mass						
fat mass/height	0.325	0.0005	0.38	<0.0001	0.216	0.021
lean mass/height	0.317	0.0007	0.37	0.0001	0.246	0.009
Appendicular skeletal mass						
total	0.316	0.0007	0.36	0.0001	0.226	0.016
percent lean	-0.19	0.041	-0.22	0.018	-0.12	0.197
Bone mineral density						
Cervical spine	0.28	0.002	0.31	0.0007	0.19	0.036
Trochanter	0.26	0.004	0.30	0.001	0.185	0.046
Intertrochanter	0.257	0.006	0.27	0.003	0.228	0.014
Total hip	0.28	0.002	0.30	0.001	0.22	0.017
Lumbar spine	0.265	0.004	0.29	0.002	0.245	0.008
Neuropsychological						
MMSE	0.024	0.71	0.077	0.235	0.059	0.363
TMT-A	-0.07	0.464	-0.07	0.444	-0.063	0.515
TMT-B	-0.08	0.398	-0.085	0.388	-0.03	0.76
TMT-B:TMT-A	-0.13	0.18	-0.146	0.138	0.002	0.982
CESD	-0.10	0.114	-0.12	0.057	-0.15	0.018

CRP = C-reactive protein; sIL2r = soluble interleukin 2 receptor; sIL6r = soluble interleukin 6 receptor; sTNFr1 = soluble tumour necrosis factor receptor 1; sTNFr2 = soluble tumour necrosis factor receptor 2; BMI = body mass index; BADL = Basic activities of daily living; IADL = Instrumental activities of daily living; YPAS = Yale Physical Activity Survey; MMSE = Mini Mental State Examination; TMT-A = trail making test part A; TMT-B = trail making test part B; CESD = Center for Epidemiologic Studies Depression Scale.

Table 4

Multiple regression model for the prediction of log total testosterone (T) in African-American women aged 49 – 65 years. Data presented are correlation coefficients (β -coef) and associated standard error (S.E.) and P-values for each factor in the model. Model statistics show the final number of observations (N), the predictive value of the model (Adj. R^2) and associated P-value

Log T Model Factor	β-coef.	S.E.	P
<i>Log DHEAS</i>	<i>0.557</i>	<i>0.116</i>	<i>0.000</i>
<i>Log SHBG</i>	<i>-0.428</i>	<i>0.158</i>	<i>0.008</i>
PT/bw knee ext (120°)	-0.008	0.008	0.316
Lean mass/height	0.00001	0.00002	0.593
BMD total hip	0.0278	0.589	0.638
Meds_Beta-blocker	0.227	0.264	0.393
Meds_Estrogen	-0.128	0.221	0.565
<i>Model Statistics</i>			
N	99		
Adj. R^2	0.38		
P	< 0.0001		

DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone-binding globulin; PT/bw = peak torque/body weight; BMD = bone mineral density.

Table 5

Multiple regression model for the prediction of log free androgen index (FAI) in African-American women aged 49 – 65 years. Data presented are correlation coefficients (β -coef) and associated standard error (S.E.) and P-values for each factor in the model. Model statistics show the final number of observations (N), the predictive value of the model (Adj. R^2) and associated P-value

Log FAI Model Factor	β -coef.	S.E.	P
Log DHEAS	0.818	0.152	0.000
Log adiponectin	-0.356	0.172	0.042
PT/bw knee ext (120°)	-0.016	0.013	0.223
PT/bw ankle ext (120°)	0.014	0.032	0.662
Lean mass/height	0.00003	0.00003	0.23
BMD total hip	-0.267	0.819	0.745
Meds_Beta-blocker	0.218	0.358	0.545
Meds_Estrogen	-0.920	0.274	0.001
Model Statistics			
N	99		
Adj. R^2	0.42		
P	< 0.0001		

DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone-binding globulin; PT/bw = peak torque/body weight; BMD = bone mineral density.

Table 6

Multiple regression model for the prediction of log dehydroepiandrosterone sulfate (DHEAS) in African-American women aged 49 – 65 years. Data presented are correlation coefficients (β -coef) and associated standard error (S.E.) and P-values for each factor in the model. Model statistics show the final number of observations (N), the predictive value of the model (Adj. R^2) and associated P-value

Log DHEAS Model Factor	β-coef.	S.E.	P
Age	-0.019	0.014	0.187
Log T	0.328	0.064	0.000
Log CRP	0.063	0.054	0.250
Log sTNFr2	-0.153	0.141	0.280
IADLs	-0.094	0.043	0.034
Lean mass/height	0.00001	0.00002	0.509
BMD total hip	-0.077	0.45	0.865
Meds_Beta-blocker	-0.217	0.187	0.249
Meds_CCB	0.368	0.126	0.004
CESD	-0.287	0.131	0.031
<i>Model Statistics</i>			
N	111		
Adj. R^2	0.38		
P	< 0.0001		

T = testosterone, CRP = C-reactive protein; sTNFr2 = soluble tumor necrosis factor receptor 2; IADL = Instrumental activities of daily living; BMD = bone mineral density; CCB = calcium channel blockers; CESD = Center for Epidemiologic Studies Depression Scale.