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CLINICAL PRACTICE GUIDELINE

Androgen Therapy in Women: An Endocrine Society Clinical Practice Guideline

Margaret E. Wierman, Rosemary Basson, Susan R. Davis, Sundeep Khosla, Karen K. Miller, William Rosner, and Nanette Santoro

University of Colorado at Denver and Health Sciences Center (M.E.W.), Aurora, Colorado 80010; University of British Columbia (R.B.), Vancouver, Canada V6T 1Z4; Alfred Hospital/Monash University (S.R.D.), Melbourne, Victoria 3181, Australia; Mayo Clinic (S.K.), Rochester, Minnesota 55905; Massachusetts General Hospital (K.K.M.), Boston, Massachusetts 02114; St. Luke's/Roosevelt Hospital Center (W.R.), New York, New York 10019; and Albert Einstein College of Medicine (N.S.), Bronx, New York 10461

Objective: The objective was to provide guidelines for the therapeutic use of androgens in women.

Participants: The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee (CGS) of The Endocrine Society, six additional experts, a methodologist, and a medical writer. The Task Force received no corporate funding or remuneration.

Evidence: The Task Force used systematic reviews of available evidence to inform its key recommendations. The Task Force used consistent language and graphical descriptions of both the strength of recommendation and the quality of evidence, using the recommendations of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group. The strength of a recommendation is indicated by the number **1** (strong recommendation, associated with the phrase "we recommend") or **2** (weak recommendation, associated with the phrase "we suggest"). The quality of the evidence is indicated by cross-filled circles, such that ⊕◯◯◯ denotes very-low-quality evidence, ⊕⊕◯◯ low quality, ⊕⊕⊕◯ moderate quality, and ⊕⊕⊕⊕ high quality. Each *recommendation* is followed by a description of the *evidence.*

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions during one group meeting, several conference calls, and e-mail communications. The drafts prepared by the task force with the help of a medical writer were reviewed successively by The Endocrine Society's CGS, Clinical Affairs Committee (CAC), and Executive Committee. The version approved by the CGS and CAC was placed on The Endocrine Society's web site for comments by members. At each stage of review, the Task Force received written comments and incorporated needed changes.

Conclusions: We recommend against making a diagnosis of androgen deficiency in women at present because of the lack of a well-defined clinical syndrome and normative data on total or free testosterone levels across the lifespan that can be used to define the disorder. Although there is evidence for short-term efficacy of testosterone in selected populations, such as surgically menopausal women, we recommend against the generalized use of testosterone by women because the indications are inadequate and evidence of safety in long-term studies is lacking. A review of the data currently available is presented, and areas of future research are outlined. To formulate clinical guidelines for use of testosterone in women, additional information will be necessary. This includes defining conditions that, when not treated with androgens, have adverse health consequences to women; defining clinical and laboratory parameters that distinguish those with these conditions; and assessing the efficacy and long-term safety of androgen administration on outcomes that are important to women diagnosed with these conditions. This necessary clinical research cannot occur until the biological, physiological, and psychological underpinnings of the role of androgens in women and candidate disorders are further elucidated. (***J Clin Endocrinol Metab* 91: 3697–3710, 2006**)

SUMMARY OF EVIDENCE-BASED GUIDELINES ON THE THERAPEUTIC USE OF ANDROGENS IN WOMEN

1. Diagnosis

1.1 We recommend *against* making a diagnosis of androgen deficiency in women at this time because there is neither a well-defined clinical syndrome nor normative data on testosterone or free testosterone levels in women across their lifespans that can be used to define the disorder (**1**|⊕◯◯◯).

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DISCLAIMER: Clinical Practice Guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of healthcare providers and each patient's individual circumstances.

Abbreviations: BMD, Bone mineral density; CAIS, complete androgen insensitivity syndrome; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; DHT, dihydrotestosterone; FAI, free androgen index; Kd, dissociation constant; MT, methyltestosterone; OCP, oral contraceptive pill.

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2. Treatment

2.1 Although evidence exists for short-term efficacy of testosterone in selected populations, such as surgically menopausal women, we recommend *against* the generalized use of testosterone by women because the indications are inadequate and evidence of safety in long-term studies is lacking (**1**|⊕◯◯◯).

To formulate clinical recommendations, the task force would require additional data 1) defining conditions that, when not treated with androgens, have adverse health consequences to women; 2) defining clinical and laboratory parameters that distinguish those with these conditions; and 3) assessing the efficacy and long-term safety of androgen administration on outcomes that are important to women diagnosed with these conditions.

This necessary clinical research cannot occur until the biological, physiological, and psychological underpinnings of the role of androgens in women and candidate disorders are further elucidated. Thus, the task force makes the following recommendations to the clinical and research community.

3. Needed Assays

3.1 We recommend the development of sensitive and specific assays to accurately measure testosterone and free testosterone in women across their lifespans (**1**|⊕⊕⊕◯).

4. Needed Research

4.1 We recommend additional research in the following human model systems to define the clinical syndrome of androgen deficiency and to study the benefits and risks of androgen therapy (**1**|⊕◯◯◯):

- Surgical menopause is a condition in which the ovarian, but not adrenal androgen, precursors are removed abruptly independent of age.
- Hypopituitarism can be used to study the physiological replacement of ovarian and adrenal androgens precursors.
- Anorexia nervosa may be used as a model of androgen deficiency secondary to dysfunction of the hypothalamic-pituitary and adrenal axes.
- Primary adrenal insufficiency allows for the investigation of the loss of adrenal androgen precursors in the presence of intact ovarian androgen function.
- Ablation-replacement models in normal women using GnRH analogs to eliminate ovarian androgens, with or without suppression of adrenal androgen precursors, offer another way to assess the effects of androgen withdrawal and replacement.
- Subjects with complete androgen insensitivity syndrome offer a way to investigate target tissue effects that are dependent on the androgen receptor but are independent of aromatization.
- There are studies in patients with low weight and HIV and with natural aging; however, these systems are too complex to recommend as initial models to understand the potential therapeutic role of androgens in women.

4.2 We recommend additional investigation using rodents and primates to further define the specific targets of androgen action (**1**|⊕◯◯◯).

4.3 We recommend additional research into the role of local androgen production, action, and metabolism in tissues (**1**|⊕◯◯◯).

4.4 We recommend the further study of physiological targets of androgen action such as (**1**|⊕◯◯◯):

- Sexual dysfunction
- Cognition
- Mood
- Bone
- Cardiovascular function
- Body composition
- Muscle strength and function

4.5 We recommend the following endpoints be considered for safety and risk assessment of androgen administration (**1**|⊕◯◯◯):

- Appearance of or change in hirsutism, acne, male pattern balding, clitoromegaly, and deepening of the voice.
- Cardiovascular and metabolic evaluation, with and without estrogen replacement, should include fasting lipid profiles, vascular reactivity, markers of insulin sensitivity, and markers of inflammation.
- Effects on the breast, with or without estrogen replacement, should be measured. Breast biopsy studies with *in vitro* markers of cell proliferation and apoptosis should be considered.
- Alterations in the endometrium with and without estrogen coadministration.
- Alterations in mood using validated instruments.

METHOD OF DEVELOPMENT OF EVIDENCE-BASED GUIDELINES

The CGS of The Endocrine Society identified "androgens in women" as a topic of importance for practice guidelines and appointed a six-member expert panel to formulate evidence-based recommendations. The Task Force elected to use the approach recommended by the GRADE group, an international group with expertise in development and implementation of evidence-based guidelines (1). The Task Force reviewed the available literature to inform its key recommendations and used consistent language and graphical descriptions of both the strength of recommendation and the quality of evidence. The strength of a recommendation is indicated by the number **1** (strong recommendation, associated with the phrase "we recommend") or **2** (weak recommendation, associated with the phrase "we suggest"). The quality of the evidence is indicated by cross-filled circles, such that ⊕◯◯◯ denotes very-low-quality evidence, ⊕⊕◯◯ low quality, ⊕⊕⊕◯ moderate quality, and ⊕⊕⊕⊕ high quality. Each *recommendation* is followed by a description of the *evidence.*

Although high-quality evidence measuring patient-important outcomes is lacking to allow for broadly applicable recommendations for diagnosis and treatment of androgen deficiency in women in clinical practice at this time, the panel felt strongly that this is an important area of clinical and scientific interest. On the basis of this review, the panel has outlined recommendations for needed research to allow future recommendations on diagnosis and treatment.

1. Diagnosis

1.1.A RECOMMENDATION

We recommend against making a diagnosis of androgen deficiency in women at this time because there is neither a well-defined clinical syndrome nor normative data on testosterone or free testosterone concentrations in blood in women across their lifespan that can be used to define the disorder.

1.1.B EVIDENCE

Research related to therapeutic use of androgens in women has been hampered by a lack of a clear definition of a syndrome and by inadequate endocrine measurements and poor outcome tools. Neither a clear definition nor clear clinical syndromes are attributable to androgen deficiency in women. In addition, the assays to measure androgens have not been optimized to measure the low levels found in premenopausal or postmenopausal women. Because total testosterone concentrations are modulated by SHBG, which in turn is modulated by estrogens, free testosterone levels would be a better measure of androgen status. However, to date, few assays have the sensitivity or specificity to measure free testosterone levels in women, especially menopausal women. Thus, if normative data are lacking across the lifespan, it is difficult to use an endocrine assay to define "deficiency." Moreover, serum levels may not reflect intracellular testosterone production from adrenal and ovarian prohormones.

2. Treatment

2.1.A RECOMMENDATION

Although evidence exists for short-term efficacy of testosterone in selected populations, such as surgically menopausal women, we recommend against the generalized use of testosterone by women because the indications are inadequate and evidence of safety in long-term studies is lacking (**1**|⊕○○○).

2.1.B EVIDENCE

In the United States, testosterone therapy is not approved for use in women for "androgen deficiency." Some compounding pharmacies and over-the-counter products, however, have bypassed this restriction by providing personalized androgen replacement. Problems with this approach include the lack of quality assurance for the androgenic substances sold in compounding pharmacies or products at health food stores. The adrenal and ovarian precursor hormones dehydroepiandrosterone (DHEA) and androstenedione are not considered true androgens because they do not bind to and activate the androgen receptor. In addition, the metabolism and actions of these precursors is complex. Because both DHEA and androstenedione are prohormones, and can be converted to testosterone and/or dihydrotestosterone (DHT), as well as to estrogens, the tissue-specific actions may be androgenic and/or estrogenic. Studies using a nonaromatizable androgen would more directly assess androgen *vs.* estrogen action at various targets. Studies using depot formulations of testosterone in pellets and injectable forms showed pharmacological plasma androgen levels that are neither approved nor safe for women. Furthermore, most interventional studies to date have been in estrogen-replete subjects; dose-response characteristics of testosterone in the absence of endogenous estrogens are needed. Finally, there are no data on the safety and efficacy of physiological testosterone administration in women beyond 24 wk. The data concerning administration of prohormones such as DHEA or androstenedione are even weaker and will not be discussed in detail. Because of these deficiencies, the Task Force recommends against the use of testosterone therapy in women until further research is completed. In this document, we summarize the available research to date and areas where investigation is needed.

3. Needed Assays

3.1.A RECOMMENDATION

We recommend the development of sensitive and specific assays to measure testosterone and free testosterone in women across their lifespans (**1**|⊕⊕⊕○).

3.1.B EVIDENCE

Androgens in plasma

All assays of analytes in plasma must meet criteria of sensitivity, specificity, and reproducibility. The problem in the measurement of testosterone in plasma is the difficulty of quantifying very small concentrations in the presence of steroids with closely related structures. The issue is compounded when evaluating the very low levels of free testosterone. In women, only about 1–3% of testosterone is free in the blood, the remainder being bound to SHBG (~65–75%) and albumin (~25–35%) (2).

Measurement of total testosterone

The advent of RIA for testosterone (3, 4) addressed the problems of sensitivity and specificity in the measurement of this hormone in biological fluids. The creation of high-affinity antibodies and the use of radioactive labels allowed detection of extraordinarily small concentrations of testosterone. However, barring the use of an extraction step, which increases sensitivity, the achieved sensitivity is inadequate for measurement of levels in women. Furthermore, when the same sample is analyzed using a number of different proprietary assays, some of which use unextracted serum, significantly different answers are obtained for both men and women (5, 6). At the low concentration of testosterone in the plasma of women, the values have little utility (5, 6). Realization of this problem has fostered the development of nonimmunoassay technology that involves chromatography, followed by sequential mass spectroscopy (MS/MS) (7, 8).

Free testosterone

In plasma, testosterone circulates bound to two proteins, SHBG and albumin (9). That which is unbound, free testosterone, is often thought of as being the moiety that has access to the cell and results in androgenic effects. In truth, the situation is more complicated (10, 11); but, as a practical matter, free testosterone often correlates better with the androgenic state of the patient than does total testosterone. In addition, there exists the concept of bioavailable testosterone,

defined as the concentration of testosterone that is free together with that which is weakly bound, *e.g.* the albumin-bound fraction, or simply non-SHBG-bound testosterone. It must be realized that any measure of free testosterone, or its surrogates, depends on the quality of the assay for total testosterone. Assuming that the total testosterone assay is at optimal sensitivity and specificity, there are several alternative approaches to estimate free testosterone. Still, one is attempting *ex vivo* to approximate an *in vivo* concept.

Measurement of free testosterone. There are three general ways to measure free testosterone *in vitro* (8, 12): 1) separate free testosterone and assay it; 2) add radiolabeled testosterone to plasma *in vitro*, separate the free radioactivity from that which is bound, and multiply the fraction free by the assayed total testosterone done in a separate assay; and 3) perform a direct immunoassay. The first two methods are technically difficult but can give reproducible and accurate answers—limited mainly by the ability to measure total testosterone accurately and specifically (13). These methods depend neither on having an accurate assay for SHBG nor on knowing the dissociation constant (Kd) for the testosterone-SHBG interaction. However, neither method allows approximation of so-called bioavailable testosterone. The third method, direct immunoassay, although simple and relatively inexpensive, should *not* be used because the values it generates are extraordinarily inaccurate (13, 14). Under development are methods based on chromatography followed by tandem mass spectrometry sensitive enough to measure free testosterone (7).

Measurement of bioavailable testosterone. Bioavailable testosterone refers to that fraction of testosterone in plasma that can enter cells. This fraction is widely defined as the free plus albumin-bound testosterone. The SHBG-bound testosterone is not "bioavailable." However, the concept is too simplistic, because in some tissues SHBG-bound testosterone is available and in others it is not (10), an issue that is a concern with any method used. The method depends on the precipitation *in vitro* of radiolabeled testosterone bound to SHBG and the multiplication of the fraction in the supernatant (albumin-bound and free) by total testosterone. The main difficulty with this process is that it is poorly standardized (15).

Free testosterone index (testosterone/SHBG). Because free testosterone depends heavily on testosterone and SHBG, there is a reasonable correlation between this measurement and free testosterone. However, free testosterone depends not only on the ratio, but also on the absolute concentration of both testosterone and SHBG (16).

Calculation of free testosterone. One can use the law of mass action to calculate free testosterone and the concentration that is bound to SHBG and albumin (17, 18). The calculation depends on the measurement of total testosterone, total SHBG, and total albumin and on the use of the Kd between SHBG and testosterone and between albumin and testosterone. There is no difficulty with the albumin portion of the calculation (18). Although the Kd for SHBG-testosterone is about 10^{-9} M, this number needs to be verified and universally agreed upon. SHBG is an abundant protein that is not difficult to measure; however, different kits and methods use a different standard, thus yielding discrepant results. A universal standard is needed so that results between labs can be compared. With those caveats, calculation of free testosterone is a practical estimate of free testosterone in plasma (18, 19), and it can be performed using the published equations (17, 18). Again, the major obstacle is the ability to measure total testosterone to use in the equation.

4. Needed Research

There is currently no established definition of androgen deficiency in women on which to base clinical care. Such definitions presuppose standard, valid assays and normative data that are only now being developed (see *3. Needed Assays*). Additional data are necessary to establish a definition of a clinically relevant androgen deficiency syndrome—one that is based on measurable deleterious clinical effects attributable to androgen deficiency, in association with low androgen levels in women.

4.1.A RECOMMENDATIONS

We recommend additional research in the following human model systems to define the clinical syndrome of androgen deficiency and to study the benefits and risks of androgen therapy (**1**|⊕◯◯◯):

- *Surgical menopause is a condition in which ovarian androgens, but not adrenal androgen precursors, are removed abruptly, independent of age.*
- *Hypopituitarism, although uncommon, can be used to study the physiological replacement of both ovarian androgens and adrenal androgen precursors.*
- *Women with anorexia nervosa have altered hypothalamic-pituitary suppression of ovarian and adrenal androgen precursors.*
- *Primary adrenal insufficiency allows the investigation of adrenal androgen precursor replacement with intact ovarian androgen function.*
- *Subjects with complete androgen insensitivity syndrome offer a way to investigate target tissue effects which are dependent on the androgen receptor but are independent of aromatization.*
- *Patients with HIV and low body weight have been used to evaluate the impact of androgen deficiency.*
- *Glucocorticoid- and oral contraceptive (OCP)-induced suppression of endogenous androgens are additional paradigms to examine the effects of androgen deficiency.*
- *Ablation-replacement models in normal women using GnRH analogs to remove ovarian androgens, with or without inhibition of adrenal secretion, offer another way to assess the effects of androgen withdrawal and replacement.*
- *Normal aging represents the ultimate relevant clinical scenario; there have been some cross-sectional and a few longitudinal studies, but the complexities of aging make it an unsuitable model for initial studies to carefully dissect the physiological role of androgens in women.*

4.1.B EVIDENCE

Surgical menopause

Bilateral oophorectomy results in the loss of ovarian androgen and androgen precursor production (20) in both post-

menopausal and premenopausal women. The plasma concentrations of the major androgenic products of the ovaries are lower in postmenopausal oophorectomized women than in postmenopausal nonoophorectomized women (21). Thus, women with surgical menopause provide a model in which to study the efficacy of androgen therapy in women deprived of ovarian androgens. To optimize such studies, several issues should be considered. Investigators must ensure that women are matched by age and years since oophorectomy, as these factors may affect the clinical response to the intervention. Use of physiological estrogen therapy, by a parenteral route, should be considered in studies of estrogen with and without androgen to avoid the biochemical perturbations induced by oral estrogen therapy. Finally, subanalyses based on the initial indication for oophorectomy should be performed, as these factors may affect the ultimate efficacy of hormonal therapy. A recent study confirmed that perimenopausal women choosing elective hysterectomy and bilateral salpingo-oophorectomy over hysterectomy alone for benign disease did not show any deterioration in sexual function (22).

Hypopituitarism

Hypopituitarism in women results in compromised adrenal and ovarian function and is associated with very low plasma concentrations of androgens, including testosterone, free testosterone, androstenedione, and DHEA sulfate (DHEAS) (23). Hypopituitarism is therefore a useful condition in which to study the effects of replacement strategies on severe androgen deficiency in women. There is only a single randomized, placebo-controlled study of the effects of testosterone administration in women with hypopituitarism. In estrogen-replete, androgen-deficient women receiving testosterone patch compared with placebo, Miller *et al.* (24) showed an increase in hip and radial, but not spine, bone density. Thigh muscle mass, fat-free mass, mood, and sexual function as well as some aspects of quality of life improved, but there was no improvement in cognitive function (24). Arlt *et al.* (25) demonstrated improvements in sexual function, libido, and mood in a small randomized placebo-controlled study of DHEA, 50 mg daily, in women with adrenal insufficiency of primary or secondary origin. Three subsequent small, randomized, placebo-controlled studies of DHEA replacement (20–50 mg/d) in women with hypopituitarism (26–28) also reported improvements in quality of life; one (27) also found improved sexual function and another (28) found improved mood. However, these effects were generally small, and two other studies of women with adrenal insufficiency demonstrated no improvements in well-being (29, 30) with DHEA administration. Changes in body composition (29, 31) and bone density (27) have been investigated in a few studies of DHEA therapy, with only one demonstrating a statistically significant decrease in percentage of fat mass (29).

Anorexia nervosa

There are few data on androgen deficiency in women with anorexia nervosa. One 3-wk placebo-controlled trial in 33 androgen-deficient women with anorexia nervosa demonstrated increases in procollagen I carboxy-terminal propeptide (PICP), a bone formation marker, as well as improvements in mood and spatial cognition (32). In this same pilot study, mood also improved in depressed women with anorexia nervosa (32). DHEAS levels were decreased in women with anorexia nervosa (33). There have been no long-term placebo-controlled studies of the effects of testosterone administration in this population.

Adrenal insufficiency

Adrenal insufficiency is characterized by low DHEA and its metabolites, including testosterone (34). Arlt *et al.* (34) demonstrated a beneficial effect of DHEA in women with adrenal insufficiency (see *Hypopituitarism*). Several subsequent randomized, placebo-controlled studies of DHEA replacement in adrenal insufficiency have shown less consistent results (see *Hypopituitarism*) (28–31, 35).

Subjects with complete androgen insensitivity syndrome (CAIS)

Patients who have estrogens but are androgen resistant represent an uncommon but informative group. If androgens have a significant physiological role at various targets independent of estrogens, individuals with this syndrome would be predicted to have significant deficits. To date, little information is available. In one study of 22 subjects with CAIS, psychosexual adjustment did not differ from that of control women (36). In a long-term follow-up of subjects with CAIS, patients reported satisfaction with the female gender and sexual function (37); however, a recent assessment of 66 women with CAIS, who had had vaginal reconstruction, reported that 90% had sexual complaints, including infrequent intercourse and difficulties with vaginal penetration (38). The latter problem may be due to lack of adequate surgical vaginal reconstruction in such women, rather than an effect of androgen status.

Low-weight subjects with HIV

Lower mean androgen levels were observed in two studies of HIV-positive women compared with healthy controls (39, 40). However, placebo-controlled trials failed to demonstrate substantial increases in weight or muscle mass or alterations in neuropsychological endpoints in women with AIDS wasting who were given transdermal testosterone (150–300 μg daily) (41, 42). One randomized, placebo-controlled trial demonstrated an increase in strength in women receiving testosterone, compared with those receiving placebo, after 6 months of treatment (43).

Exogenous suppression of androgens

Glucocorticoid administration is associated with a rapid and marked suppression of DHEA, DHEAS, androstenedione, testosterone, and DHT in women (25). Such women are potential candidates for the study of androgen replacement. Administration of testosterone to glucocorticoid-treated men (44) has beneficial effects on measures of bone and body composition, but no data regarding women are available.

It has been suggested that some OCPs suppress ovarian

androgen production sufficiently to cause decreases in libido (45). However, it may not be the contraceptive alone that is responsible for a woman's decreased libido; psychological factors may contribute. It therefore becomes challenging to tease apart the role of other factors from androgen suppression in the alteration in libido of women taking OCPs (46, 47). Nonetheless, OCPs suppress total and free testosterone levels in women with polycystic ovarian syndrome to those seen in eumenorrheic women without polycystic ovarian syndrome (48), and in normal women levels are suppressed to below normal (23). Women on OCPs might provide a useful, albeit complex, group for studying effects of androgens. The androgenicity of the progestin in the OCP studied, as well as the effects of certain OCPs on body composition and SHBG (49), would need to be considered as confounding issues in this model.

Ablation-replacement paradigms in normal subjects

Women can have their ovarian steroid production suppressed with GnRH analogs with or without blockade of adrenal hormone secretion. The administration of aromatizable and nonaromatizable androgens to such subjects would provide a more precise definition of the dose-response relationships of androgens, as well as the possible role of conversion to estrogens in the responses in various target tissues. Aromatization by adipose tissue may increase with age and, thus, may affect plasma and cellular concentrations of estrogens (50, 51); controls for these variables should be included in future investigation.

Aging

DHEAS in plasma decreases with increasing age (52–54). Cross-sectional data indicate an approximately 80% decline from age 20 to age 80 yr. Because DHEAS is a stable marker of adrenal prohormone production, it typically has been used as the "gold standard" single measure. However, in the limited investigations performed to date, DHEA and other adrenal metabolites appeared to undergo an identical trajectory (53). Recent data from the Study of Women's Health Across the Nation (SWAN) (55), as well as data from nonhuman primates (56), indicate that natural menopause was associated with a brief rise in DHEA and DHEAS, although this finding was not shown in other databases.

Ovarian androgens do not decline dramatically with natural menopause. The data on circulating and bioavailable testosterone during the menopausal transition are not uniform. Four cohort studies have examined androgens in detail in naturally menopausal women. Rannevik *et al.* (57) studied 160 Swedish women longitudinally through the menopausal transition. Small but significant decreases in testosterone were observed. Decreases in SHBG were associated with increasing body mass index. DHEAS decreased over time, without acceleration at menopause.

The Massachusetts Women's Health Study (58), derived from a population-based sample of largely Caucasian women, reported results in 88 women sampled at 4- to 6-month intervals over a 10-yr period. A significant decline in DHT and DHEAS was observed, with a rise in androstenedione associated with traversal of the menopause (58). Similar results were seen in a smaller longitudinal study of 32 women (59). The Melbourne Healthy Women's Study (60) sampled blood across the menopausal transition in 172 of 450 women. There was no annual decrease in testosterone over the course of the transition, but an increase in free androgen index (FAI) was observed as was a decreasing SHBG. No support for a menopause-related decrease in ovarian androgens was found. SWAN, a multicenter, community-based cohort of 3302 women of five different ethnicities, reported baseline and 2-yr follow-up data on androgens (61). Women in SWAN were aged 42–52 yr at baseline, and all were relatively estrogen replete, with at least one menstrual period within the past 3 months. Initial and 2-yr follow-up of serum testosterone found no correlation of testosterone with menopausal status. Testosterone and FAI were noted to be strongly positively correlated to the presence of the metabolic syndrome at baseline and were less strongly correlated to self-rated health, well-being, and sexual desire and arousal. Testosterone and FAI were negatively correlated to Center for Epidemiological Studies-Depression Scale (CES-D) scores; DHEAS was directly correlated to higher physical functioning and self-rated health (62). Most of these population studies used commercially available kit assays for the measurement of total testosterone; these assays are known to have limited sensitivity and accuracy at lower values. Thus, interpretation of the normative data in the literature must be viewed as preliminary until more sensitive assays are validated.

The published data indicate a progressive, substantial, age-related decline in DHEAS. There is minimal evidence to support a decline in testosterone associated with the menopause transition *per se*; only one of the four cohorts described above reported a slight but statistically significant decline (57). If circulating hormones are meaningful indicators of biological activity, then the natural menopause cannot be conceptualized as an ovarian androgen-deficiency state. However, testosterone levels do decline substantially from the mid-reproductive years (21, 63) such that, relative to women in their twenties, women in their forties have an approximately 50% reduction in plasma testosterone. This process occurs before the menopausal transition, and its etiology is unclear. Because of the complexities of the process and the limitations of current testosterone and free testosterone assays, women with natural menopause would not be an optimal model in which to initially investigate testosterone replacement, yet this is the population to which most investigational data are intended to be applied.

4.2.A RECOMMENDATION

We recommend additional investigation using rodent and primate models to further define the specific targets of androgen action (**1**|⊕○○○).

4.2.B EVIDENCE

Animal or cell models are needed to define potential markers of androgen action. Although certain endpoints of androgen action [*e.g.* bone mineral density (BMD) or turnover, body composition, *etc.*] are relatively easy to assess in humans, potential effects of androgens on brain function or

sexual responses are much more subjective and difficult to evaluate. The development of potential markers of such responses (*e.g.* using specialized brain-imaging techniques) in these animal models would greatly aid further research in the area of androgen's effects on brain and sexual function in women.

4.3.A RECOMMENDATION

We recommend additional research into the role of local androgen production, action, and metabolism in tissues (**1**|⊕○○○).

4.3.B EVIDENCE

Steroids are secreted and may act as such or be converted in target tissues to an active principle. For example, testosterone is both a hormone (*i.e.* acts as such in tissues such as muscle) and a prohormone (*i.e.* is converted into DHT) (64), which is the active principle in tissues such as skin. This situation is further complicated by the occurrence of small fractional conversions of steroids, present in high concentrations in plasma, *e.g.* DHEA and DHEAS, to yield biologically relevant amounts of active hormones, *e.g.* testosterone (65–67). Furthermore, if the testosterone that arises in cells from plasma precursors is additionally metabolized within those cells, without passing through the plasma, then we have no current measure of these effects. In addition, this tells us that hormone action may be influenced not only by the secretion, clearance, and plasma binding of testosterone, but also by the activity of enzymes within cells that convert it into an active metabolite that may change with physiology, pathology, and age. That these events occur is unquestionable. How relevant they are to our understanding of androgen therapy for women is unclear. There are pathological states, *e.g.* androgenic alopecia in women, with normal plasma testosterone, where we assume the hypersensitivity of the scalp to normal concentrations of circulating testosterone is based on such mechanisms, *e.g.* increased activity of 5α-reductase. We currently have no method to evaluate such mechanisms in the normal woman who is hypothesized to be hypoandrogenic and, therefore, for the moment, we must proceed in clinical decision making with the use of plasma-based assays.

4.4.A RECOMMENDATION

We recommend further study of physiological targets of androgen action (**1**|⊕○○○) *such as:*

- *Sexual dysfunction*
- *Cognition*
- *Mood*
- *Bone*
- *Cardiovascular function*
- *Body composition*
- *Muscle strength and function*

4.4.B EVIDENCE

Sexual dysfunction

Testosterone therapy at supraphysiological dosing in animals and humans is associated with increased arterial flow-mediated dilatation (68), vaginal blood flow (69, 70), and vaginal smooth muscle contractility (71). Large clinical studies, which included 2961 and 1021 women across the lifespan, indicate that serum levels of testosterone using current assays (free, calculated free, total, or bioavailable) do not correlate with sexual function (52, 62). Difficulties in interpretation arise from the lack of accuracy of the assays, a lack of consensus on the optimal time for measuring testosterone during the menstrual cycle, and a lack of consensus on the definition of sexual function and measurement instruments. Finally, the inability to measure testosterone produced within target cells from precursors is an issue that cannot be addressed with current methodology.

Women's sexual dysfunctions result from the interplay of many personal, interpersonal, contextual, and medical factors (77–80). In any one woman, changes in androgens may or may not be relevant. Apparent "dysfunction" frequently results from adaptation to a nonconducive psychosocial milieu, often with no defect in the woman's physical sexual response system (77, 81, 82). Four factors have been shown to correlate robustly with women's sexual function/satisfaction: the woman's mental and emotional health including her sexual self-image (77, 78, 83); her feelings for her partner both at the time of sexual interaction and in general (77, 84); her expectations regarding the future of the relationship (85, 86); and her past sexual experiences (84). Other factors showing strong correlation include the woman's perception of her general health (87), her perceived level of stress (85), her partner's sexual function (88), and the duration of the relationship (84, 89).

Studies of testosterone therapy to date have excluded women with depression, problematic relationships, poor health, and partners with sexual dysfunction, yet these comorbidities are common. Studies are needed in which, along with optimal hormonal evaluation, these psychosocial factors are carefully examined. The interaction between these underlying issues and response to exogenous testosterone warrants exploration.

To date, the main evidence that testosterone has a role in women's sexual function comes from the benefit of testosterone supplementation in surgically menopausal women complaining of sexual dysfunction. Of the 24 separate trials before November 2003 addressing testosterone treatment, five recruited women with sexual dysfunction, nine reported effects on sexual function, and only three provided data suitable for meta-analysis—two of these involved methyl testosterone and one involved testosterone implants (reviewed in Ref. 90). Two of the reviewed studies involved transdermal testosterone, and the remainder used either methyl testosterone or injectable testosterone to achieve plasma levels exceeding the upper limits of normal in younger women (91–98).

Four subsequent studies used transdermal testosterone given to estrogen-replete oophorectomized women and achieved testosterone levels at the upper end of the normal range for young healthy women in the assay used (99–102). One trial of transdermal testosterone in naturally menopausal women has been reported (103). Using validated unpublished questionnaires, all five studies showed a significant increase in desire and response scores, and four showed significant reductions in distress scores. After 24 wk of trans-

dermal testosterone patch therapy, there were small but significant correlations observed among changes in serum total, bioavailable, and free testosterone and the frequency of satisfying sexual activity (Spearman's rank correlation of 0.16 to 0.18; $P < 0.05$). For sexual desire, the correlations with total and free testosterone were 0.20 to 0.25 ($P < 0.05$), and for personal distress the correlation was −0.11 to −0.17 ($P < 0.05$) (100). Only one study was dose ranging, and the data suggest a dose-response relationship (100). Similarly, in the trial in which all women used transdermal estradiol patches, serum total and free testosterone and DHT correlated with desire, arousal, orgasm, pleasure responsiveness, and the number of satisfying sexual events (101). Although modest, there were also statistically significant correlations between testosterone levels and multiple aspects of sexual response in the study of naturally menopausal women (103). The overall size of the effect is small in these studies, resulting in approximately one more episode of satisfying sexual activity per month compared with controls. However, after exclusion of women using conjugated equine estrogens from the analysis, the effect size was increased to a mean of two more episodes per month compared with controls (Procter & Gamble Pharmaceuticals, FDA Advisory Committee Briefing Document NDA 21-769; available at http://www.fda.gov/OHRMS/DOCKETS/AC/04/briefing/2004-4082B1_01_A-P&G-Intrinsa.pdf). The benefit over placebo was observed with the 300-μg, but not the 150- or 450-μg, patch administered biweekly.

Despite the documented benefit of transdermal testosterone in estrogen-replete women, there are two major factors precluding its recommendation for broad use. Because women initiating therapy may wish to remain sexually active indefinitely (104), the lack of long-term safety data of testosterone therapy and the reservations about long-term estrogen therapy preclude recommendation. There are no data regarding the sexual benefit of transdermal testosterone in estrogen-deficient women at present.

The second major reason is the lack of a clear definition of the "disorder." The recent trials recruited women diagnosed with "hypoactive sexual desire disorder." The definition of this entity assumes that sexually satisfied women initiate or accept sexual activity for reasons of desire. This is not evidence based (73, 105–108). Thus, further work is ongoing to reassess the official definitions of women's sexual dysfunction (81, 82, 109–112).

Definitions of women's sexual dysfunction

"Hypoactive sexual desire disorder" is defined in the *American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders*, Text Revised (DSM-IV-TR) (113) as follows: "Persistently recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician, taking into account factors that affect sexual functioning, such as age and context of the person's life, the disturbance causes marked distress or interpersonal difficulty." Of note, the DSM-IV-TR definition is the same for women as for men. However, lack of desire at the outset of sexual engagement is common for sexually content women and sexual thoughts are infrequent in many women without sexual complaints (77). Furthermore, the frequency of sexual fantasies has little correlation with women's sexual satisfaction (77, 86).

Randomized controlled trials have not yet been conducted in women using the recently revised definition of sexual desire/interest disorder defined as "absent or diminished feelings of sexual interest or desire, absence of sexual thoughts or fantasies, *and a lack of responsive desire.* Motivations (here defined as reasons/incentives) for attempting to become sexually aroused are scarce or absent. The lack of interest is considered to be beyond the normative lessening with lifecycle and relationship duration" (81). The revised definition clarifies that lack of spontaneous or initial desire is not of itself dysfunctional; rather, it is the additional inability to become aroused, to sense pleasure and trigger *responsive* desire during the sexual encounter that constitutes disorder. Of note, the recent testosterone-patch trials reported increases not only in desire but also in arousal, pleasure, and orgasmic response. It would, therefore, be important to study women recruited on the basis of the new definitions of desire/interest disorder: the focus would be on restoring subjective arousal and pleasure such that desire is triggered during the sexual experience and not on "spontaneous/initial" desire. The latter is more typically present at the beginning of new relationships (89) and is known to have a broad range of frequency across sexually satisfied women (72) as well as to lessen gradually with age. Because all recent randomized controlled trials have used testosterone rather than a nonaromatizable androgen, it is unclear whether the sexual benefit is ultimately conferred by an androgen or an estrogen. However, one recently published study indicates that the effect may not require aromatization (101).

Need for industry-independent studies of female sexual dysfunction

There is a need for non-industry-funded research into female sexual health, the physiological role of androgenic steroids, and the efficacy and safety of pharmacotherapy. Such industry-independent randomized placebo-controlled trials should recruit women diagnosed with sexual desire/interest and arousal disorders consonant with the current definitions of women's sexual disorders. The focus would then be on women for whom no sexual experiences are satisfying. Given the confirmed multifactorial nature of women's sexual function and dysfunction, both hormonal and nonhormonal factors should be carefully investigated. Women receiving testosterone therapy must receive long-term follow-up, with the expectation that therapy will be open-ended.

Cognition

Tests of cognition should be sensitive to subtle changes that fall within the average range of performances. Unfortunately, most tests of cognition were not developed to measure subtle changes in cognitively intact persons. In addition, the repeated administration of the same tests leads to some improvement in performance in healthy participants. For example, improvement in total learning over five trials of the California Verbal Learning Test (CVLT) is well documented

(115). Only tests shown to have minimal practice effects can be readministered repeatedly, yet few validated tests of cognition meet this requirement. Finally, if aromatizable androgens are administered, the effects on specific cognitive outcome measures change across the day as the androgen is converted into estrogens (116).

Few studies have investigated the effects of exogenous testosterone on cognition. Of these, several did not randomize for estrogen replacement in postmenopausal women, although testosterone was given randomly. Many of the studies have been underpowered, and cognitive measurement used only subscales of validated instruments. It is highly likely, therefore, that the finding of a single improvement in score on one test was a chance finding. Androgen doses typically have been large, resulting in supraphysiological plasma levels. Thus, the available evidence does not demonstrate a consistent effect, the methodology often has been invalid, and the generalizability of the data is unknown.

In two studies of premenopausal women, improvements in specific aspects of cognitive function have been reported after a single supraphysiological dose of testosterone (117, 118). Specifically, improvements in visuospatial memory were reported after a dose of 0.5 mg testosterone was administered sublingually; the assessment was undertaken shortly thereafter. Although testosterone levels were not measured in either study, the authors report that this dose was associated with a 10-fold increase in total testosterone levels within 15 min of intake. Such levels are supraphysiological for women and approximate those in men.

In postmenopausal women, two studies of methyltestosterone (MT) reported improvements in isolated cognitive tasks (119, 120). Wisniewski *et al.* (120) reported no statistically significant difference between treatments for visuospatial memory but reported maintenance of the Building Memory Task score for the MT-treated group. In a double-blind cross-over study, Regestein *et al.* (119) reported a significant benefit of MT on the Switching Attention Test.

In a cross-over study, there was no effect on cognitive function of supraphysiological intramuscular injections of estrogen plus testosterone *vs.* estrogen alone (121). A 3-wk randomized placebo-controlled study demonstrated that transdermal testosterone (150–300 μg) resulted in improvements in spatial cognition in women with anorexia nervosa (32). In a subset of these subjects, positron emission tomography (PET) scans showed improvements in brain hypometabolism in the posterior cingulate cortex after testosterone administration. These salutary changes were associated with improvements in spatial cognitive testing (32). Such experiments provide an example of a quantifiable outcome that is amenable to serial measurement.

Mood

No studies using validated psychiatric tools have specifically investigated the effects of testosterone or DHEA administration on mood in depressed women. Mood has been investigated as a secondary endpoint in several small studies in other populations. These populations include women of reproductive age with bilateral oophorectomy (122), sexual dysfunction (123), or anorexia nervosa (32).

Bone

With the use of new, high-sensitivity testosterone assays, both trabecular and cortical BMD have been recently shown to be associated with serum bioavailable testosterone levels, particularly in late postmenopausal women (124). There are no data on the effects of androgen replacement in women on the risk of fracture. Relatively small studies, using BMD as a fracture surrogate, are inconsistent. Two studies comparing oral estrogens or estrogens plus androgens (125) or estradiol and estradiol plus testosterone implants (126) in postmenopausal women found no significant effect of added testosterone on spine or hip BMD. By contrast, three studies comparing oral estrogens and oral estrogens plus androgens (127), sublingual estradiol with estradiol plus testosterone (128), or estradiol implants with estradiol plus testosterone implants (94) showed that the addition of testosterone therapy to estrogen replacement enhanced increases in spine and/or hip BMD. One study in estrogen-replete women with androgen deficiency associated with hypopituitarism showed increased BMD at the hip and radius but not spine (24). Bone resorption markers decrease similarly with estrogen alone or combined with testosterone (128, 129); there may be a short-term (over 9 wk) maintenance (or increase) of bone formation markers with the addition of testosterone (129) as compared with estrogen alone (128, 129). The clinical relevance of this difference in terms of changes in BMD or fracture risk remains unknown. Only one randomized placebo-controlled study investigated the effect of transdermal testosterone on bone markers in the absence of estrogen administration. Procollagen I carboxy-terminal propeptide (PICP), a bone formation marker, increased over 3 wk in women with anorexia nervosa (32). The clinical relevance of the differences in the markers, in terms of changes in BMD or fracture risk, remains unknown.

Cardiovascular function

Effects on lipoproteins. Dissecting the possible role of sex steroids in cardiovascular disease (CVD) due to alterations in lipoproteins is complex. Understanding the relationships between SHBG and the CVD risk factors is critical in determining whether androgens in women contribute to CVD risk. SHBG is produced by the liver and is a pivotal determinant of the concentration of free sex steroids (130). Estrogens increase, whereas androgens and insulin decrease, SHBG concentration in plasma (131). Insulin has been shown to be a strong independent marker of insulin resistance (132, 133). Several studies have demonstrated that low SHBG is associated with increased CVD risk and coronary disease mortality in women and men (134–137).

Numerous studies have reported an association among the FAI, CVD risk factors, and the metabolic syndrome (135, 137–139). The nature of the underlying relationships and mechanisms for them remain unknown. In a study of 200 women not using hormone therapy, lower SHBG and higher FAI levels were noted among postmenopausal women who developed CVD events; however, this was not statistically significant after adjusting for body mass index and other cardiovascular risk factors (140). Additional outcome studies are needed to identify the strength of the relationship be-

tween SHBG, insulin resistance, and CVD end points in women, as well as mechanistic studies capable of teasing out the independent contributions of androgens, should they exist.

Other surrogate markers for vascular function. Studies of the effects of exogenous androgens on lipids have involved the administration of oral MT or transdermal testosterone. These different modes of testosterone administration result in different effects on lipoproteins. Oral MT (2.5 mg) has consistently been associated with a reduction in high-density lipoprotein cholesterol (90, 141), whereas this has not been observed with transdermal testosterone (32, 42, 122, 142). MT also has been associated with reductions in triglycerides but with inconsistent findings with respect to total cholesterol and low-density lipoprotein cholesterol (90).

Other surrogate markers for the effects of testosterone on the cardiovascular system include effects on endothelial function, carotid intima-media thickness, and coronary artery calcification, among others. Research on these surrogate vascular markers in women has been mostly limited to studies of women with polycystic ovarian syndrome. Because this is not simply a condition of androgen excess but also involves an intrinsic insulin resistance, findings from these studies cannot be extrapolated to the use of exogenous androgens or endogenous androgen effects in otherwise healthy women. One open-label study of flow-mediated blood vessel dilation in women, with and without testosterone implants with or without pharmacologically induced testosterone levels, showed no adverse effects of testosterone treatment on this measure of endothelial function (68). Additional data are needed on the effects of physiological testosterone administration on vascular markers in women.

Body composition

Three studies have found that addition of testosterone to conjugated estrogen replacement resulted in greater increases in fat-free mass (143, 144). Davis *et al.* (143) found that fat-free mass increased by 12.5% in the estrogen plus testosterone group but remained unchanged in the estrogen alone group, and Dobs *et al.* (144) found that lean body mass increased by 1.2 kg with estrogen plus testosterone therapy as compared with only a 0.4-kg increase with estrogen alone. In one of these studies (143), testosterone appeared to attenuate the reduction observed in central body fat with estrogen alone. Thus, although estrogen administration decreased the ratio of fat mass to fat-free mass in a region directly over the abdomen (as measured by dual-energy x-ray absorptiometry), this effect was lost in the group treated with estrogen plus testosterone. Miller *et al.* (24) demonstrated increases in thigh muscle area by cross-sectional computed tomography.

Muscle strength and function

In two studies, transdermal testosterone treatment (300 μg) in women with AIDS led to no increase in fat-free or muscle mass (41, 43); one (43) showed increases in strength. One randomized, placebo-controlled study of 40 postmenopausal women demonstrated increases in fat-free mass and increased strength in those receiving esterified estrogen plus MT (1.25 mg estrogen + 2.5 mg MT/d) compared with esterified estrogen alone (1.25 mg/d; Ref. 144). One randomized, placebo-controlled study demonstrated an increase in lean body mass with nandrolone decanoate plus caloric restriction compared with caloric restriction alone in obese postmenopausal women (145). More data are needed.

4.5.A RECOMMENDATION

We recommend the following endpoints be considered for safety and risk assessment in future studies (**1**|⊕○○○):

- *Alterations in the endometrium after androgen administration, with and without estrogen coadministration.*
- *Effects of androgen therapy on the breast with or without estrogen replacement should be measured, including mammographic density. Breast biopsy studies with in vitro markers of cell proliferation and apoptosis should be considered.*
- *Cardiovascular and metabolic end points should include fasting lipid profiles, vascular reactivity, fasting glucose and insulin levels, and inflammatory markers such as adiponectin and C-reactive protein.*
- *Hirsutism, acne, male pattern balding, and change in voice should be monitored.*

4.5.B EVIDENCE

Endometrium

It is widely believed that androgens, acting through classical androgen receptor mechanisms, are antiproliferative in the human endometrium. In support of this hypothesis, evidence from a study using mixed progesterone agonists suggests that these agents mediate endometrial atrophy by up-regulating the androgen receptor (146). Endometrial adenocarcinoma growth is prevented by androgens, and the presence of androgen receptors appears to be associated with reduced proliferation (147). Although endometrial hyperplasia would appear to be unlikely in women taking exogenous androgens, the endometrium should be monitored in an adequately powered randomized control trial.

Breast

Androgens, acting through the androgen receptor, oppose estradiol-induced proliferation of human breast cancer cell lines (148). Zhou *et al.* (149) have demonstrated androgen-induced down-regulation of mammary epithelial proliferation and estrogen receptor expression in primates. Clinically, women with elevated androgen levels, either endogenous or exogenous, experience breast atrophy, consistent with the notion that androgens *per se* are antiproliferative for the breast. However, advanced proliferative premalignant breast lesions are known to have enhanced local aromatase (150, 151), and the possibility exists that aromatization of exogenous androgens could contribute to breast cancer risk for women taking them.

If one looks at polycystic ovarian syndrome as a model of androgen excess, the risk of breast cancer is not increased despite hyperandrogenism and long-term exposure to unopposed estrogens (74, 75). In fact, Gammon and Thompson (75) reported an age-adjusted odds ratio for breast cancer in women with this syndrome of 0.52 (95% confidence interval,

0.32 to 0.87). In postmenopausal women, there are inconsistent results as to the relation of testosterone levels to breast cancer risk in both cross-sectional studies and prospective studies. Limitations of the studies include use of insensitive assays, measurement of only total testosterone, and failure to take into consideration the diurnal variation of testosterone when drawing blood (114). Thus, the evidence pertaining to the use of testosterone therapy and breast cancer risk has significant methodological limitations and inconclusive results (114).

Cardiovascular and metabolic function

Metabolic safety parameters that should be evaluated in future clinical trials include lipids, fasting glucose, and insulin. Effects on inflammatory markers such as C-reactive protein should be assessed.

Side effects on skin and voice

Hirsutism, acne, male pattern balding, and deepening of voice should be monitored. Most recent studies using doses of testosterone that result in free testosterone in or near the normal range for women report no increase in hirsutism, acne, or virilizing side effects with short-term administration (42, 99, 100, 102, 122). However, data in this regard are limited by sample size, the failure of many studies to report the presence or absence of side effects, lack of objective measures, and short study duration. Monitoring of facial and body hair is limited by the common use of depilatory techniques. Therefore, frequency of depilation may be a more sensitive end point to detect increases in hirsutism. For example, Shifren *et al.* (122) found no increases in hirsutism when measured by the Lorenzo scale but detected an increase in depilatory rates, compared with baseline, in women receiving transdermal testosterone at 300 μg daily. Importantly, long-term effects (>1 yr) of androgen administration in women on these outcomes have not been established.

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Address all questions to: The Endocrine Society, 8401 Connecticut Avenue, Suite 900, Chevy Chase, Maryland 20815. E-mail: govtprof@endo.society.org. Telephone: 301-941-0200. Address all reprint requests for orders 101 and more to: Heather Edwards, Reprint Sales Specialist, Cadmus Professional Communications, Telephone: 410-691-6214, Fax: 410-684-2789 or by E-mail: endoreprints@cadmus.com. Address all reprint requests for orders 100 or less to Society Services, Telephone: 301-941-0210 or by E-mail: societyservices@endo-society.org.

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