EVEXIAS HEALTH SOLUTIONS

Androgen Assays and Clinical Application: White Paper

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Androgen (testosterone) deficiency

has been implicated as a vital contributory factor in many chronic conditions such as coronary heart disease, metabolic syndrome and diabetes, desire disorders in women, and mental and physical aging in both sexes. The primary androgenic sex hormone made in the gonads, and to a lesser extent the adrenals, in both sexes is testosterone.

Testosterone therapy (TRT)

in men and women has been utilized in various modalities to address vague symptomatology and improvement in overall quality of life since the 1930's. The oldest and longest studied modality of TRT is subcutaneous pellet implants, followed by injectable testosterone and topical creams respectively.

A key aspect of androgen therapy in both sexes that eludes standardization is the measurement of serum androgen assays both as a baseline and after a therapy is initiated. The Endocrine Society has established general guidelines (opinion based not founded in clinical data) for diagnosing androgen deficiency in males, however the literature does not support utilizing absolute hormone measurements for the diagnosis and subsequent management of testosterone replacement in either sex. In females, there are no established reference ranges for androgens or other sex hormones due to cyclical and other variables, therefore guidelines for diagnosing and managing androgen therapy in women is nonexistent. Historically, management of hormone therapy in women has been solely based on symptom presentation and subsequent relief thereof. It is vital to comprehend there are no established normal levels of serum testosterone in either sex, there are simply expected ranges based on the population of the laboratory data, and every lab has different expected ranges of total and free testosterone.

There are several reasons standardization of therapy utilizing absolute hormone levels do not exist.

Reason 1

First and foremost, the available modalities, subcutaneous, transdermal, injectable, and oral routes all vary in absorption, metabolism, and subsequent receptor site activation. A key concept to understand when initiating therapy is serum testosterone is a measurement of the inactive hormone, it must convert to the active hormone metabolites. Each modality has varying degrees of conversion into the active hormone metabolites, dihydrotestosterone, and estradiol, and each patient has various physiological factors (BMI, activity levels, co-morbidities, other medications, etc.) that play a role in metabolism and excretion of the hormone metabolites. Free testosterone levels, the available androgen for metabolism and action in the body, are dependent on multiple factors, most notably the level of sex hormone binding globulin (SHBG), a protein that binds up available free testosterone, rendering it inactive.

Reason 2

Although in both sexes the literature supports the use of a free testosterone level as a more reliable indicator of androgen status, the lower tertile of the reference range correlates with symptom presentation and the upper tertile is associated with symptom relief; some patients report symptom relief only with higher-than-expected (supraphysiologic) free testosterone levels. Further, there is no standardization of free testosterone assays or expected reference ranges across laboratories.

Reason 3

Lastly, there are no long-term safety studies found in the literature that conclude higher levels of testosterone, when monitored appropriately, produce sentinel or adverse events. The literature does conclude the nuisance side effects of "supraphysiologic" serum levels of testosterone in both sexes to be variable and reversible when therapy dose is reduced or discontinued.

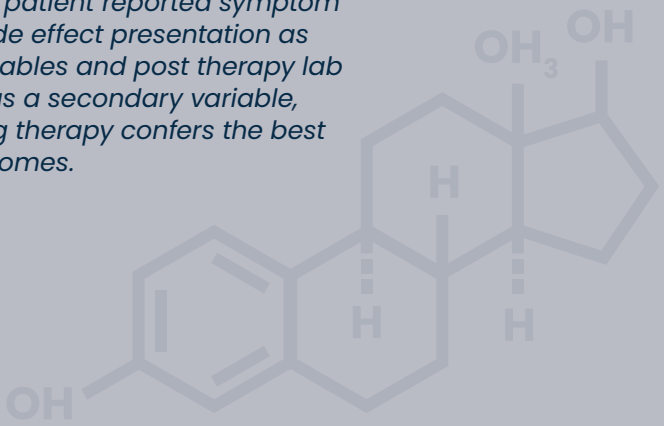
The succeeding cited literature will address two key concepts regarding androgen assays and testosterone therapy in both sexes:

Concept 1

Utilizing androgen assays, both free and total, as a baseline measurement that, when correlated with symptom presentation, is useful for initiating therapy.

Concept 2

Utilization of patient reported symptom relief and side effect presentation as primary variables and post therapy lab evaluation as a secondary variable, in managing therapy confers the best clinical outcomes.



I

Carruthers M, Trinick TR, Wheeler MJ (2007).
The validity of androgen assays.
The Aging Male, 10:165-172.

Problems in the measurement of androgens and in interpreting results have been reviewed and classified as follows:

Preanalytical factors

The exact sampling conditions in relation to circadian and seasonal variations, diet, alcohol, physical activity and posture.

Physiological and medical factors

Androgen levels vary according to the patient's general health, stress, sexual activity and smoking habits.

Analytical variables

Sample preservation and storage variables are often unknown.

The different androgen assays used have widely differing accuracy and precision and are subject to large inter-laboratory variation, which especially in women and children can render the results of routinely available direct immunoassays meaningless.

Interpretation of results

Laboratory reference ranges vary widely, largely independent of methodology, and fail to take into account the log-normal distribution of androgen values, causing errors in clinical diagnosis and treatment.

Other unknowns are antagonists such as SHBG, estrogens, catecholamines, cortisol, and anti-androgens. As well as age, androgen receptor polymorphisms play a major role in regulating androgen levels and resistance to their action.

Conclusions: Though laboratory assays can support a diagnosis of androgen deficiency, they should not be used to exclude it. It is suggested that there needs to be greater reliance on the history and clinical features, together with careful evaluation of the symptomatology, and where necessary a therapeutic trial of androgen treatment given.

II

Carruthers, M. (2008).
The paradox dividing testosterone deficiency symptoms and androgen assays: a closer look at the cellular and molecular mechanisms of androgen action. The Journal of Sexual Medicine, 5(4), 998-1012.

- There is a poor correlation between symptoms of androgen deficiency (or "excess") and serum testosterone levels.
- Neither total nor free testosterone nor bioavailable testosterone are definitive measures of patient outcomes or response to treatments.
- The variable responses to testosterone levels are based on several aspects of androgen deficiency (or "excess") and how it metabolizes and exerts its action in the cell:
  - Impaired androgen synthesis or regulation.
  - Increased androgen binding.
  - Reduced tissue responsiveness.
  - Decreased androgen receptor activity.
  - Impaired transcription and translation.

III

Bachmann, G., Bancroft, J., Braunstein, G., Burger, H., Davis, S., Dennerstein, L., ... & Traish, A. (2002).
Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. Fertility and Sterility, 77(4), 660-665.

- Current androgen assays are unsatisfactory primarily because of their lack of sensitivity or reliability.
- The consensus statement on female androgen insufficiency: There are no established "normal" levels of testosterone in women.

IV

Shufelt, C. L., & Braunstein, G. D. (2009).
Safety of testosterone use in women. Maturitas, 63(1), 63-66.

- Short-term studies, up to 2 years, have shown that for serum plasma testosterone levels at the upper portion or above (supraphysiologic) the reference range for reproductive- aged women, testosterone does not increase the risk of hepatotoxicity, endometrial hyperplasia, or behavioral hostility.
- No adverse cardiovascular effects including changes in blood pressure, blood viscosity, arterial vascular reactivity, hypercoagulable states, and polycythemia have been shown.
- As with all hormone therapy, testosterone therapy should be individualized and not based on absolute lab values.

V

Panay, N., & Fenton, A. (2009).
The role of testosterone in women. Climacteric, 12(3), 185-187.

Maclaran, K., & Panay, N. (2012).
The safety of postmenopausal testosterone therapy. Women's Health, 8(3), 263-275.

- Testosterone has been used therapeutically in women for over 70 years.
- The implanted pellets of testosterone have been available in many countries for many decades.
- Many of the early studies reported on the use of injectable, oral or implant therapy, often in supraphysiological doses.

- Testosterone is now most frequently administered via subcutaneous implant or transdermal gel/cream.
- The testosterone implants have been used for over 30 years and there are both observational and randomized controlled trial (RCT) data that women receiving estradiol and testosterone implants have a significant benefit in sexual function, mood, quality of life and overall sense of well-being compared with those receiving estrogen alone.
- Although testosterone replacement can have significant benefit, an ongoing concern frequently cited by regulatory authorities and consensus statements is the apparent uncertainty surrounding the long-term safety of testosterone, especially regarding the risk of breast or endometrial cancer and cardiovascular disease. As presented in the literature, these concerns are unfounded.

- At these doses reports of nuisance side effects (hair growth, acne) are both reversible with adjustments in doses and subsequent levels.

- Androgenic side effects tend to be dose dependent, may take several months to become evident, but are usually mild and resolve when treatment is discontinued or dose decreased.

- Virilization–voice deepening, clitoromegaly and frontal hair loss–is extremely rare.

- In a long-term study of 1094 women receiving testosterone therapy, no increase in the rates of androgenic adverse events (unwanted hair growth, acne, alopecia or voice deepening) over 4 years of treatment, and reported events were generally mild and not associated with study discontinuation.

VI

Rivera-Woll, L. M., Papalia, M., Davis, S. R., & Burger, H. G. (2004).

Androgen insufficiency in women: diagnostic and therapeutic implications. Human Reproduction Update, 10(5), 421-432.

- Reduced libido, diminished well-being, anxiety and depressed, lowered mood, brain fog, memory impairment, joint pain, insomnia are all symptoms of androgen insufficiency.

- Diagnosis is based on these symptoms in the setting of a low (lower quintile of reference range) serum free testosterone level or lower quintile of total testosterone level.

- Currently no readily available inexpensive assay which reliably measures free testosterone levels in females.

- Further complicated by the lack of data demonstrating a minimum serum free testosterone level which, if below this, correlates with the symptoms.
- Despite the complexities involved with defining FAIS, symptoms have been reported to respond well to testosterone replacement.
- Ongoing treatment and monitoring of testosterone replacement should be based on clinical response and not absolute lab levels.

VII

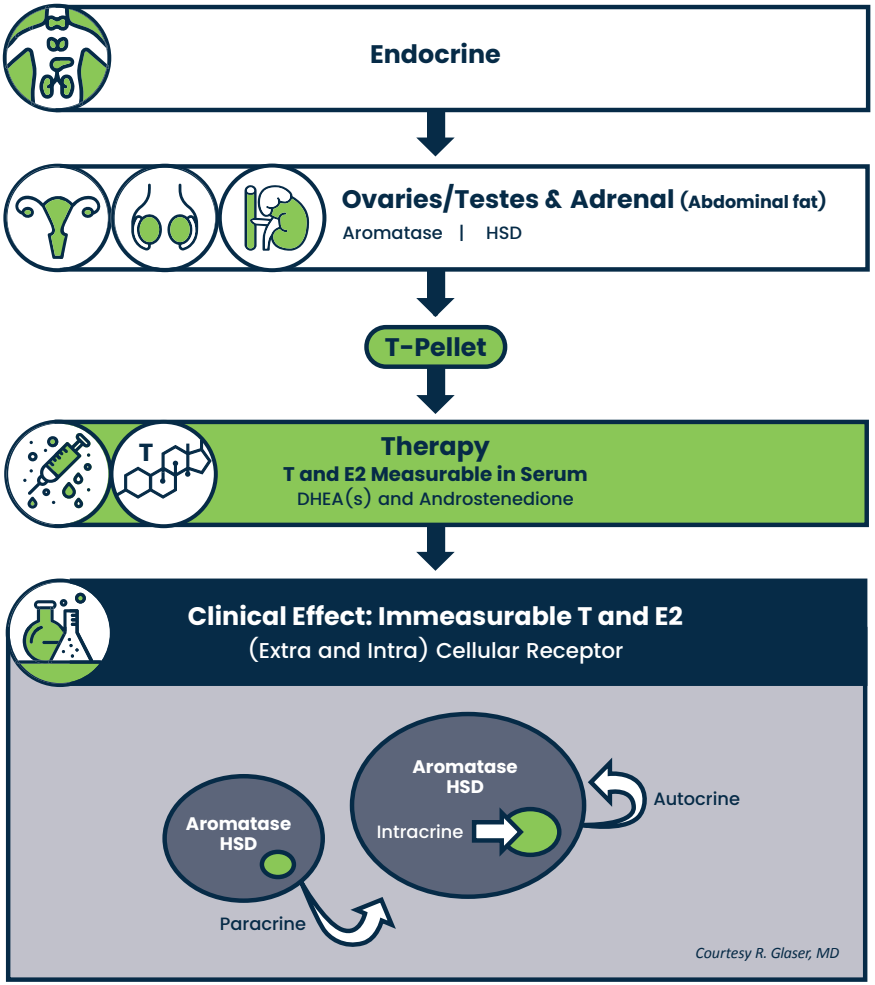
Glaser, R., Kalantaridou, S., & Dimitrakakis, C. (2013).
Testosterone implants in women: pharmacological dosing for a physiologic effect. Maturitas, 74(2), 179-184.

- The objectives of this study were to determine therapeutic serum testosterone (T) levels/ranges and inter-individual variance in women treated with subcutaneous T implants.
- In this clinical practice, over 16,000 T pellet insertions have been performed in over 1300 female patients.
- On average the total serum T levels in these patients ranged from 150 to over 300 ng/dl.
- We have previously reported on the benefits and safety of T delivered by sustained release implants with an average starting dose of 2 mg/kg.
- We have observed, that some symptoms (e.g., bone pain, memory loss, neurological complaints and tremor) and some diseases (e.g., multiple sclerosis, Parkinson's disease and Alzheimer's disease) require higher dosing (4 mg/kg) for optimal clinical effect.

There have been no reported adverse drug events attributed to T therapy other than expected androgenic side effects, which are reversible with lowering T dose. Many patients prefer the clinical benefits of higher doses/levels of T and choose to take care of the side effects of therapy.

Conclusions: Pharmacologic dosing of subcutaneous T, as evidenced by serum levels on therapy, is needed to produce a physiologic effect.

Safety, tolerability and clinical response should guide therapy rather than a single T measurement, which is extremely variable and inherently unreliable.



VIII

Pastuszak, A. W., Mittakanti, H., Liu, J. S., Gomez, L., Lipshultz, L. I., & Khera, M. (2012).
Pharmacokinetic evaluation and dosing of subcutaneous testosterone pellets. Journal of Andrology, 33(5), 927-937

- Subcutaneous testosterone (T) pellets are a viable treatment modality for hypogonadism.
- Optimal dosing and frequency of reimplantation T pellets remain incompletely elucidated parameters.
- Subcutaneous T pellets resulted in a rise and decay in serum T levels and peak T levels were a function of the number of pellets implanted and patient BMI but not of the preimplantation serum T level or the order of implantations.

IX

Barbonetti, A., D'Andrea, S., & Francavilla, S. (2020).
Testosterone replacement therapy. Andrology, 8(6), 1551-1566.

- The aim of testosterone replacement therapy (TRT) is to improve symptoms and signs of testosterone deficiency including decreased libido, erectile dysfunction, depressed mood, anemia, loss of muscle and bone mass, by increasing serum testosterone levels.
- TRT has been used in the last 70 years, and overtime, numerous preparations and formulations have been developed to improve pharmacokinetics (PKs) and patient compliance.
- The routes of delivery approved for use in the Western world include buccal, nasal, subdermal, transdermal and intramuscular (IM).
- Each route varies in serum levels, duration or levels, absorption, metabolism, clinical outcomes and symptom relief.

- TRT is associated with multiple benefits highly relevant to the patient. However, the recommendations given in different guidelines on TRT are based on data from a limited number of randomized controlled trials (RCTs), as well as nonrandomized clinical studies and observational studies.

Conclusion: Clinicians must consider the unique characteristics of each patient and make the necessary adjustments in the management of androgen deficiency in order to provide the safest and most beneficial results.

X

Shoskes, J. J., Wilson, M. K., & Spinner, M. L. (2016).

Pharmacology of testosterone replacement therapy preparations. Translational Andrology and Urology, 5(6), 834.

- When considering all available routes of delivery, concentrations, and branded or generic choices, there are currently over 30 different testosterone preparations to consider when choosing one for a patient.
- There are no standard guidelines for baseline assessment and ongoing monitoring of treatment with TRT; the decision on the best modality should include patient clinical response and preference, PKs, treatment burden, cost and insurance coverage.
- Serum markers post therapy as well as patient response vary among modalities and are poorly correlated.
- Based on clinical response to an individual modality, products may need to be switched throughout TRT based upon patient response, preference, and adverse effects.

Conclusion: In all circumstances, the decisions should be an open dialogue between the patient and clinician to allow for the most successful TRT regimen.

XI

Morgentaler, A. (2016).

Controversies and advances with testosterone therapy: a 40-year perspective. Urology, 89, 27-32.

- There is consensus that candidates for treatment with testosterone therapy (TTh) should have signs or symptoms of testosterone deficiency (TD) combined with biochemical evidence of low T levels. The challenge is deciding what T level is considered low. For the first 40 years after the commercial availability of T products, the diagnosis was made entirely on clinical presentation.

- With the introduction of readily available testing with the development of radioimmunoassays in the 1970s, the emphasis shifted to documentation of low blood levels.

- Today, it is becoming increasingly clear that symptoms and clinical presentation should once again take priority, with blood test results a secondary confirmation not only in diagnosis, but also treatment response and management.

- The difficulty with arriving at a reasonable threshold value for biochemical confirmation of TD, either at baseline or post therapy initiation, is underscored by the wide range of recommended thresholds offered by various professional groups and experts.

- This confusing situation is worsened by the recommendation by the Endocrine Society in 2010 to follow reference ranges provided by the laboratory performing the testosterone testing, because there is so much variation in reference ranges across laboratories that one survey revealed that 17 of 25 laboratories had different reference ranges. The same test result may be categorized as normal by one laboratory, low by another, and high by another.

- There is a substantial degree of inter-individual variability with regard to symptoms and response to treatment, due at least, in part, to two known confounders—the binding of androgen to sex hormone binding globulin and genetic variability with regard to the number of CAG repeats in the androgen receptor gene, with larger numbers of repeats associated with reduced sensitivity. This means that healthcare providers must decide on whether a course (or continuance) of treatment is indicated based on the totality of clinical presentation rather than by a blood test result alone.

Notes

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