Dr Tan & Partners

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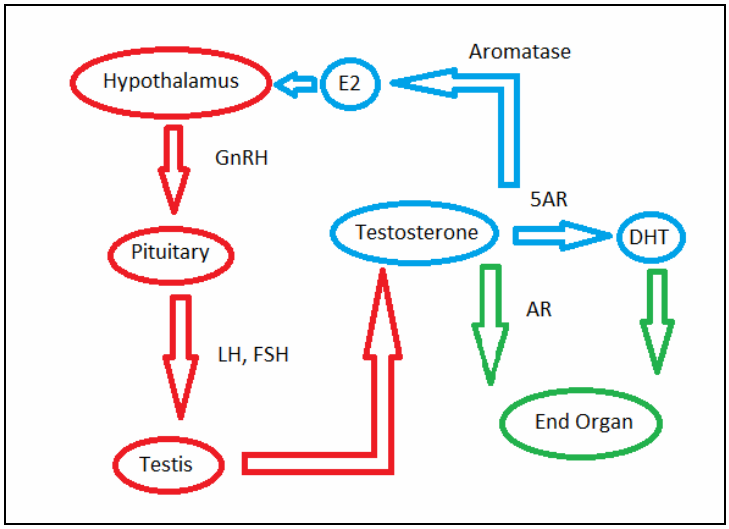
Topic
Diagnosis and Testosterone Replacement Therapy for Androgen Deficiency in the Aging Male (ADAM)

Introduction

Androgen Deficiency of the Aging Male (ADAM) is a prevalent syndrome associated with sexual dysfunction, increased risk of high grade prostate cancers, osteoporosis, metabolic syndrome and other chronic diseases. We look at its diagnosis and options for treatment.

Fundamentals of Testosterone Production



Testosterone production and homeostasis is controlled via the Hypothalamic-Pituitary-Testicular Axis. Gonadotropin released hormones are secreted by the Hypothalamus which stimulates the Pituitary gland to secrete Luteinizing hormone and Follicle stimulating hormone. These hormones stimulate the testes to produce testosterone and sperm. They are also trophic to the testes. Testosterone has a direct effect on cells but is also a pro-hormone for Estrogen (via aromatase) and Dihydrotestosterone (via 5α-Reductase).

The Pituitary gland also secretes adreno-corticotrophic hormone which stimulates the adrenals to produce testosterone. Approximately only 10% of total testosterone is produced by the adrenals.

The body produces an average of 5-7mg of testosterone per day. Of which 60% are tightly bound to Sex hormone binding globulin, 38% are loosely bound to albumin and 2% exists as free Testosterone.

Testosterone affects end organs by binding with Androgen receptors resulting in transcription of target genes.

Health Impact of ADAM

Late onset hypogonadism affects multiple organ systems. Testosterone levels drop with increasing age while SHBG increases with age. This leads to a precipitous drop in free testosterone levels with wide ranging health impacts.

LOH has been associated with decreased muscle mass and strength, increased body fat, decreased BMD and osteoporosis, decreased vitality, decreased mood, decreased frequency of morning erections, decreased libido and ED.

CV Health and Mortality

Low testosterone is a risk factor for CV-Mortality. It is also associated with increased mortality in men with coronary heart disease. In fact, low testosterone levels are associated with increased all-cause mortality

Further evidence shows testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life.

Chronic Diseases and Metabolic Syndrome

Low testosterone has been associated with Hypertension, Hyperlipidemia, Diabetes, Obesity (especially central obesity) and Asthma/COPD. In fact, low testosterone levels have been associated with an increasing number of metabolic syndrome components. BMI is inversely related to testosterone levels.

Osteoporosis

Fracture risk and osteoporosis in older men have been associated with low Estrogen and Testosterone.

Depression and Cognition

Low testosterone associated with decreased spatial memory and cognition. There is also a strong link between low testosterone and depression.

Sexual Dysfunction

Low testosterone is associated with a decrease in libido, frequency of morning erections and erectile dysfunction.

Diagnosis of ADAM

Symptoms

The symptoms of ADAM can be on-specific and are divided into:

- Sexual function
  - Decrease number of morning erections
  - Decrease libido
- Mood/Energy
  - Decline in general feeling of well-being
  - Feeling tired
  - Irritability/Nervousness/Anxiety
- Physical
  - Joint pain and muscular aches
  - Excessive sweating
  - Sleep problems
  - Decrease muscular strength
  - Decrease beard growth

The Aging Male Symptoms Questionaire can be used to semi-objectively quantify the severity of symptoms. Annex 1.

A shorter ADAM questionaire is useful for screening and diagnostic purposes. Annex 2.

Symptoms associated with ADAM are a continuum and Testosterone level correlate with symptoms:
< 15 – loss of libido and vigour
< 12 – overweight
< 10 – depression, sleeping disorders, lack of concentration, NIDDM
< 8 – ED, hot flushes

Testing

The following tests should be conducted for patients suspected of androgen deficiency:

- Screening for Hypertension, Obesity, Diabetes and Hypercholesterolaemia
- LH, FSH, Prolactin, Estradiol
- FBC, PSA – for monitoring in the event the patient has to commence TRT
- Total Serum Testosterone
  - Where possible drawn between 7:00am and 11:00am
  - Patients on testosterone gel ensure no gel is applied on the day of testing

Free Testosterone

Free testosterone gives a better indication compared to total serum testosterone of the patient's androgen status. However, there are some limitations as to the measurement of free testosterone.

Direct tests for free testosterone are only accurate if done by dialysis by equilibrium.

Since this test is costly and resource intensive, it is rarely done in commercial labs.

Calculation of free testosterone from albumin and SHBG levels have been found to have a good correlation with dialysis by equilibrium.

Interpretation of Total Serum Testosterone results

Patients whose total serum Testosterone is < 12 nmol/L with symptoms of ADAM are considered androgen deficient and should be offered TRT.

ISA, ISSAM, EAU, EAA and ASA	US Endocrine Society	EUA Guidelines
Test free T If total T < 12 nmol/L	Substitute if total T < 10.4 nmo/L	Substitute if total T < 12.1 nmo/L

Patients whose total serum Testosterone is < 16 nmol/L with symptoms of ADAM may be suffering from androgen deficiency. This is because the free testosterone could be low. Also, there exists a significant inter-individual variability in response to androgens. These patients can be offered a trial of therapy with short acting androgen preparations or undergo further testing. Further testing options include repeating the total serum testosterone another 2 times or calculating free testosterone from albumin and SHBG levels.

Where possible, start TRT with short acting Testosterone preparations. This is to allow rapid withdrawal of TRT in case of any adverse events.

Treatment Options

The only non-drug treatment that has been shown to increase total serum testosterone is weight loss.

There exist several treatment options for TRT. We discuss those that are commonly available in Singapore.

Oral Capsules

Oral capsules are convenient, painless and allow the greatest dosing flexibility.

However, they undergo a significant first pass effect and can cause hepatotoxicity. The absorption is also unpredictable as testosterone is oil soluble and the capsules have to be taken with an oily meal. There is also the problem with patient compliance.

Topical Gel

Topical gel applications for TRT are convenient and painless. They also have a lower risk of side effects from supra-physiologic doses.
However, some patients may find daily application of the gel a hassle. Also, they have to ensure the gel is not washed off their skin for 4 to 6 hours after the application. This may not suit some patients' lifestyle. There is also the risk of transfer.

3 monthly Depo-Injections

3 monthly depo-injections are convenient and there are no issues with patient compliance.

However, the injections can cause pain and the discomfort may last a day or two after the treatment. Injections also have a higher risk of causing supra-physiologic serum testosterone levels leading to suppression of spermatogenesis. Although depo-injections are designed to last 10 to 12 weeks, some patients experience a recurrence of symptoms before 10 weeks. There is also a risk of micro-emboli to the lungs during injection. Although this has not been shown to be dangerous, it can cause the patient to cough during the treatment.

Complications

Absolute contra-indications to treatment

1. Active untreated prostate cancer
2. Breast cancer
3. Fertility

TRT and PSA

TRT may cause an initial rise in PSA.

Always get a baseline PSA prior to initiating TRT.

Refer for USS Prostate or MRI Prostate if the PSA rises above 4ng/dl or the PSA velocity is > 1.4 ng/dl in 12 months.

TRT and BPH/LUTS

There is no evidence to suggest that TRT worsens BPH/LUTS. In fact, studies have shown that mild LUTS either improve or remain stable with 5 years of TRT.

TRT may also be instituted for men with BPH/LUTS who have or are undergoing surgical or medical treatment.

TRT and Prostate Cancer and PIN

There still exists a lot of controversy as to the role of Testosterone in the development of prostate cancer.

Historically, castration has been the treatment for androgen sensitive prostate cancer. This has led to a strong belief that Testosterone plays a key role in the development of prostate cancer. Recent studies seem to show otherwise.

TRT has not been shown to increase prostate cancer risk. A meta-analysis of 19 controlled TRT studies revealed no greater proportion of adverse prostate outcomes, such as increased PSA and prostate cancer compared to placebo.

A low androgen level has not been shown to be protective against prostate cancer. In fact, patients with low serum testosterone seem to develop higher grades of prostate cancer.

TRT has been safely given to patients who have undergone prostatectomy for prostate cancer.

TRT has not been associated with an increased risk of PIN developing to prostate cancer.

TRT and Heart Disease

This topic currently is very controversial due to the announcement by the US FDA in January 2014 that it was investigating the risk of cardiovascular events in patients on TRT. This comes on the back of 2 papers suggesting an association between testosterone therapy and myocardial infarction.

Since then, many doctors and experts in the field have voiced their dismay at such an action quoting multiple shortcomings of the 2 papers. There have even been a petition signed by several thousand doctors calling for the journals that published these papers to retract them.

Prior to this, there have been multiple papers published including a review paper published in the NEJM that concluded TRT has a neutral or possible beneficial effect on cardiovascular disease.

After reviewing the evidence, we recommend that TRT should be withheld pending a cardiovascular consultation for patients whom are:

1. Post CV event (MI, CVA)
2. Suffering from angina or reduced effort tolerance
3. Have multiple cardiac risk factors (smoking, diabetes, obesity)

TRT and Erythrocytosis

Testosterone replacement increases EPO levels and therefore may lead to erythrocytosis. This effect has been found to be more profound in younger men. This effect has also seen more commonly with TRT via intra-muscular injections. To date, there have been no thrombo-embolic events associated with TRT.

Haematocrit should be checked 3 months, 6 months then annually after commencement of TRT. If the HCT rises above 54%, TRT should be stopped or the formulation changed.

Follow up

Every patient on TRT should be followed up with the following tests:

1. FBC
2. PSA and DRE
3. Total serum Testosterone
4. Estradiol

Young patients with symptoms of Androgen Deficiency

Young patients who present with symptoms of Androgen Deficiency should be investigated for possible secondary causes such as:

1. Genetic conditions
    a. Klinefelters
    b. Androgen Insensitivity Syndrome (Androgen Receptor Polymorphism)
    c. Kallman's Syndrome
2. Trauma/Infection to testis
    a. Crypto-orchidism
    b. Mumps Orchitis
    c. Surgery/Radio-Therapy
3. Estrogen excess
    a. Drug/Steroid abuse
    b. Tumours
    c. Diet
4. Chronic Diseases
    a. HIV
    b. Hepatitis C
    c. Liver Cirrhosis

Warning Signs

1. Lack of secondary sexual characteristics
    a. Facial hair
    b. Musculature
    c. Flat pubic hair line
2. Abnormalities in Genitalia

   a. Low volume testis. Normal 12 to 30ml
   b. Micro-penis.
   c. Ambiguous genitalia
3. Disease Specific Signs
   a. Anosmia (Kallman's Syndrome)
   b. Wide carrying angle (Klinefelter's Syndrome)
   c. Single testis (Crypto-orchidism, previous surgery)

Summary

Androgen Dificiency is a prevalent disease among older men with potentially severe health effects. TRT is an effective management that should be offered to patients with symptoms of ADAM and documented low serum testosterone.

Practice Pointers

1. Have a high index of suspicion for ADAM in all male patients above the age of 40 years old especially if they have:
   1. Chronic diseases like DM, Hypertension, CAD, Hypercholesterolaemia
   2. Obesity
   3. Sexual dysfunction like ED
   4. Mood or sleep alterations
2. Patients with symptoms of Androgen Deficiency should undergo tests for LH, FSH, Testosterone, Estradiol and Prolactin.
3. When possible, Serum Testosterone tests should be conducted between 7:00am and 11:00am.
4. Offer TRT to patients whose total serum Testosterone is < 12 nmol/L.
5. Discuss repeat testing or trial of TRT for patients whose total serum Testosterone is < 16 nmol/L with symptoms of Androgen Deficiency.
6. Where possible, start TRT with short acting Testosterone preparations.
7. Follow up of patients should include tests for Testosterone, Estradiol, FBC and PSA.

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Annex 1

AMS Questionnaire

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none".

	Symptoms:	none	mild	moderate	severe	extremely severe
	Score =	1	2	3	4	5
1.	**Decline in your feeling of general well-being** (general state of health, subjective feeling)	☐	☐	☐	☐	☐
2.	**Joint pain and muscular ache** (lower back pain, joint pain, pain in a limb, general back ache)	☐	☐	☐	☐	☐
3.	**Excessive sweating** (unexpected/sudden episodes of sweating, hot flushes independent of strain)	☐	☐	☐	☐	☐
4.	**Sleep problems** (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)	☐	☐	☐	☐	☐
5.	**Increased need for sleep, often feeling tired**	☐	☐	☐	☐	☐
6.	**Irritability** (feeling aggressive, easily upset about little things, moody)	☐	☐	☐	☐	☐
7.	**Nervousness** (inner tension, restlessness, feeling fidgety)	☐	☐	☐	☐	☐
8.	**Anxiety** (feeling panicky)	☐	☐	☐	☐	☐
9.	**Physical exhaustion / lacking vitality** (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities)	☐	☐	☐	☐	☐
10.	**Decrease in muscular strength** (feeling of weakness)	☐	☐	☐	☐	☐
11.	**Depressive mood** (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use)	☐	☐	☐	☐	☐
12.	**Feeling that you have passed your peak**	☐	☐	☐	☐	☐
13.	**Feeling burnt out, having hit rock-bottom**	☐	☐	☐	☐	☐
14.	**Decrease in beard growth**	☐	☐	☐	☐	☐
15.	**Decrease in ability/frequency to perform sexually**	☐	☐	☐	☐	☐
16.	**Decrease in the number of morning erections**	☐	☐	☐	☐	☐
17.	**Decrease in sexual desire/libido** (lacking pleasure in sex, lacking desire for sexual intercourse)	☐	☐	☐	☐	☐

Have you got any other major symptoms? Yes ☐ No ☐

If Yes, please describe: _____

THANK YOU VERY MUCH FOR YOUR COOPERATION

Annex 2

ADAM questionnaire about symptoms of low testosterone (Androgen Deficiency in the Aging Male)

This basic questionnaire can be very useful for men to describe the kind and severity of their low testosterone symptoms.

1.	Do you have a decrease in libido (sex drive)?	Yes No
2.	Do you have a lack of energy?	Yes No
3.	Do you have a decrease in strength and/or endurance?	Yes No
4.	Have you lost height?	Yes No
5.	Have you noticed a decreased "enjoyment of life"	Yes No
6.	Are you sad and/or grumpy?	Yes No
7.	Are your erections less strong?	Yes No
8.	Have you noticed a recent deterioration in your ability to play sports?	Yes No
9.	Are you falling asleep after dinner?	Yes No
10.	Has there been a recent deterioration in your work performance?	Yes No

If you Answer Yes to number 1 or 7 or if you answer Yes to more than 3 questions, you may have low Testosterone.