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Society for Men's Health (Singapore)
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INTRODUCTION

Nomenclature

Testosterone Deficiency Syndrome (TDS) or Late Onset Hypogonadism (LOH) refers to the age-related decline in testosterone levels in ageing men, resulting in various clinical symptoms[1]. TDS may adversely affect the function of multiple organ systems and result in significant decline in the quality of life.

Other terms that are used include Androgen Deficiency in Aging Male (ADAM) and Partial Androgen Deficiency in Aging Male (PADAM).

The term Andropause has been used in medical literature and is popular with the public and mass media, as it denotes men as having "Male Menopause" or "Male Climacteric", similar to the menopause of ageing women. However, the clinical presentation and tempo of progression of TDS is different from menopause and, scientifically, the term is a misnomer.

Prevalence

As men age, the testes decline in function and testosterone secreted by them decreases. It has been reported that circulating testosterone concentration decreases by 0.4-2.0% yearly[2]. This is due to a reduction in the function and size of the Leydig cells of the testes, as well as reduced amplitude of gonadotrophin secretion[2]. This decline is exacerbated in men with obesity and men with poor health status. If men succeed in losing weight, their testosterone levels rebound[3]. In middle aged men, the incidence of TDS is found to be 6%[4].

In a longitudinal study, it was shown that by the eighth decade, 30% of men had low total testosterone and 50% had low free testosterone levels[5]. The latter is a more reliable indicator of the biological action of testosterone.

In Asian countries, the reported prevalence of hypogonadism (defined as total testosterone < 11 nmol/l) was 18.2 – 19.1%[6].

DIAGNOSIS

The diagnosis of TDS rests on the presence of suggestive clinical symptoms, and is to be confirmed by laboratory tests.

Symptoms

The most common symptom of TDS is sexual dysfunction.

Sexual Dysfunction

Erectile dysfunction, lack of libido and lack of morning erections are the most specific symptoms of TDS[7]. In men aged 40 – 79 years, the threshold for total testosterone was 8 nmol/l for decreased frequency of sexual thoughts, 8.5 nmol/l for erectile dysfunction, 11 nmol/l for decreased frequency of early morning erections[8]. Other symptoms relatively specific for androgen deficiency include hot flushes, unexplained sweating and reduced shaving frequency.

Psychological Effects

Patients may experience lack of drive, easy fatigability, irritability and mood swings. A study showed that the threshold for diminished vigour and drive occurs when total testosterone concentration is less than 13 nmol/l[9].

Somatic Effects

Patients may complain of decreased exercise capacity and muscle strength. Testosterone deficiency may lead to osteoporosis, resulting in fragility fractures.

Instruments

Instruments that document symptoms are generally not useful as screening or diagnostic tools for TDS[10].

Ageing Male Score

The ageing male score[11] is a 17 item questionnaire (Appendix I) that assesses patients' symptoms in 3 main domains – sexual, psychological and somatic. It provides a good tool to assess patients' symptoms at baseline and efficacy of treatment[12]. It is also useful in monitoring patients' response to androgen therapy.

Screening Tools

ADAM is one of the earlier instruments (Appendix II) that have been used as a screening tool for TDS[13]. As there is a great overlap of these symptoms between patients with and without TDS, they are generally not useful alone in identifying patients with TDS or for the need of treatment.

Laboratory Investigation

Testosterone Levels

As TDS is defined by the lowering of testosterone with age, serum testosterone measurement is necessary for the confirmation of TDS.

In the body, there is a diurnal variation in the serum concentration of testosterone, being highest in the early morning. In order for testosterone measurements to be accurate and consistent, testosterone levels are best measured between 7 am and 11 am[14].

Not all the testosterone circulating in the blood is immediately available to the body. Of the total amount of testosterone, only about 4% is free testosterone, which is immediately available for use by the body, with the remainder being bound to albumin and Sex Hormone Binding Globulin (SHBG), which are produced by the liver. The latter fact is important, because certain symptomatic patients with levels of total testosterone at the lower end of the normal reference range may actually have low levels of free testosterone because of a high SHBG level. This is especially so in ageing men, as SHBG tends to increase with age.

The gold standard for measuring free testosterone level is by equilibrium dialysis, which is an expensive process, and not performed commonly in commercial labs. Free testosterone measured in most commercial labs is based on analog displacement immunoassays, which is not standardized and do not bear correlation with the actual level of free testosterone. This should not be used as it gives wildly differing results[15,16].

For the physician, the most convenient way to obtain an accurate estimate of free testosterone level is to measure the serum total testosterone, albumin and SHBG, and then calculating the free testosterone level[17] by using an online calculator

on the website of International Society for Study of Ageing Male (ISSAM) at www.issam.ch. This gives a value that correlates closely with that obtained from the gold standard of equilibrium dialysis[18].

Other Hormones

Luteinizing hormone (LH) and Follicle Stimulating Hormone (FSH) should be measured to help differentiate between primary and secondary hypogonadism. Serum prolactin should be performed when secondary hypogonadism is suspected[19] or when loss of sexual interest is profound, as high prolactin levels inhibits gonadotrophin secretion.

Hormones like estradiol, growth hormone and DHEA are affected by aging. However, the significance of the changes in these hormones are not well understood, and therapy based on the levels of these hormones is controversial. It is therefore not useful to determine estradiol, growth hormone, DHEA, DHEA-S, melatonin, growth hormone and IGF-1[20].

TREATMENT

Before instituting Testosterone Replacement Therapy (TRT), a discussion with the patient regarding the rationale, benefits, risks and the need for monitoring and surveillance should be carried out. Currently, there is no arbitrary value of total testosterone or free testosterone level below which to start TRT. However, there is the general agreement that total testosterone level above 12 nmol/l (350 ng/dl) does not require TRT. There is also consensus that patients with serum total testosterone below 8 nmol/l (230 ng/dl) will usually benefit from TRT[21]. If the serum total testosterone is between 8 and 12 nmol/l, calculated free testosterone may be helpful in deciding when to commence TRT. While age-specific values of free testosterone have not been established universally (as there may be variations between different communities and populations), values below 250 pmol/L are well below the median values across all age groups[22] while values below 220 pmol/L are consistent with true androgen deficiency[7].

Suffice to say, if a patient has symptoms suggestive of TDS, together with total testosterone or free testosterone levels that suggest androgen deficiency, the patient can be considered a candidate for TRT. A 3-6 months trial period may help to establish whether TRT is helpful.

Benefits

Testosterone has many functions, in addition to its main function as a male sex hormone. It is important in the development of secondary sexual characteristics of the adolescent male. In the adult male, it is important in the maintenance of sexual function, including libido and erection. Testosterone has other physiological functions as well. It helps maintain energy levels and motivational drive. It also helps to maintain the male body habitus – greater bone mass, muscle mass and less fat as compared to the female.

Sexual Effect

TRT is beneficial in 2 aspects of sexual function – libido and erection. For patients who are refractory to Phosphodiesterase type V inhibitors (PDE5i) for treatment of erectile dysfunction, a serum testosterone should be measured to assess for TDS. A course of TRT can be instituted in those men who have low or borderline serum testosterone level.

Combined use of PDE5i and TRT has been observed to work well synergistically in patients with low or borderline serum testosterone level. This combined therapy can be considered if patients do not respond to either therapy alone[23]. Currently, the therapeutic choice for patients with Erectile Dysfunction (ED) and TDS is treatment with either PDE5i or TRT or combined therapy[24], with no evidence yet showing which the best approach is.

Psychological Effect

TRT has psychological benefits. Uncontrolled studies report improvements in energy and sense of well-being after TRT. In a small open-label trial, TRT has been reported to improve quality of life measures like sexual function, well being and mood[25]. The effects of testosterone on cognitive function are poorly understood, and some studies report small effects on visual-spatial cognition and verbal memory[26].

Somatic Effect

TRT improves body composition through the reduction in fat mass and a corresponding increase in lean body mass[27]. This in turn may lead to increase in muscle strength and function[28,29].

There is also evidence that TRT improves bone density[30]. Osteopenia, osteoporosis and fracture prevalence rates[31] are greater in patients who have low testosterone levels. However, there is no evidence as yet that TRT reduces fracture rates.

The somatic effect of TRT needs validation by larger scale studies.

Effect on Obesity, Metabolic Syndrome and Diabetes Mellitus

There is a great overlap between the symptoms and effects of TDS and metabolic syndrome (obesity, hypertension, dyslipidaemia, impaired glucose regulation, and insulin resistance[32]). Epidemiological studies have shown a close relationship between obesity and TDS[33]. Between 20%-64% of obese men have a low total or free testosterone level.

TRT has been shown to improve glycemic control in truly hypogonadal men with diabetes mellitus, although its effect on men with only relative hypogonadism is still uncertain[34,35]. Larger scale studies are needed to establish the effects of TRT on patients with metabolic syndrome and diabetes mellitus.

Risks

Risks of TRT must be discussed with the patient before starting patient on TRT. It is essential to discuss the concerns of TRT with prostate cancer, even though the link between TRT with prostate cancer is doubtful. Another common side effect of TRT is polycythemia.

Prostate Cancer

In a landmark paper published by Huggins and Hodges in 1941, it was found that patients with metastatic prostate cancer had aggravation of disease after the administration of testosterone, and castration led to a rapid decrease in serum marker acid phosphatase (a marker of prostate cancer activity before the PSA era). Since then, Androgen Deprivation Therapy (ADT) has become the mainstay in the treatment of metastatic prostate cancer. The presence of untreated prostate cancer remains an absolute contraindication to the starting of TRT[36]. There are also concerns that giving TRT to patients may activate the indolent prostate cancer that may be present. However, there is no evidence to the latter concern[37].

In a study of TRT in men with TDS, Prostate Specific Antigen (PSA) in men on TRT did not differ significantly from that in men treated with placebo[38]. In addition, meta-analysis of 19 controlled TRT studies revealed no greater proportion of adverse prostate outcomes, such as increased PSA and prostate cancer development in men on TRT[39].

Prior to starting TRT, Digital Rectal Examination (DRE) and a PSA level should be performed to detect prostate cancer. If either investigation is suspicious, referral should be made to the Urologist to assess for prostate cancer by Transrectal Ultrasound (TRUS) and biopsy of the prostate. Routine TRUS before initiation of TRT is not necessary if DRE and PSA are normal.

Patients on TRT should have regular assessment of PSA[40]. PSA can be performed initially at 3 to 6 monthly intervals, but the testing interval can be stretched to a year if stable.

Any increase of PSA to abnormal levels or at abnormal rates should warrant a urological consult, whereby a TRUS and biopsy of the prostate may be performed.

Patients with prostate cancer who have been successfully treated and who are found to have TDS may be given TRT. However, great care must be taken to establish that the patients are indeed cured of the disease with clinical and biochemical evidence of absence of prostate cancer activity[41,42,43]. While they are on TRT, they should be monitored closely for recurrence of the disease. The risks and benefits must be clearly discussed with these patients, and follow up must be particularly stringent.

Benign Prostatic Hyperplasia

There is currently no evidence that TRT will result in the enlargement of the prostate gland, worsening Lower Urinary Tract Symptoms (LUTS) secondary to Benign Prostatic Hyperplasia (BPH). In men who have been medically or surgically treated for LUTS secondary to BPH, and who are found to have TDS, TRT can be instituted for them.

Polycythemia

Testosterone stimulates erythropoiesis. Men with significant polycythemia (haematocrit > 52%) should not be given TRT before the assessment, treatment and resolution of the polycythemia.

Polycythemia can develop during TRT. Periodic assessment of haematocrit should be performed as part of the overall surveillance during TRT. The interval of surveillance can be similar to that of PSA surveillance, that is, every 3 to 6 monthly initially, and at least yearly thereafter if stable.

If the patient develops polycythemia during TRT, drug holiday can be instituted, and dosage or dosing interval can be adjusted. If severe, phlebotomy can be performed, though the critical level for this procedure is not established. Generally, it is advisable to keep the haematocrit level below 52%.

Contraindications

Untreated prostate cancer and breast cancer are absolute contraindications to the initiation of TRT. Patients who still wished to have biological fatherhood should also avoid TRT, as testosterone replacement may depress the FSH through negative feedback, resulting in decreased production of spermatozoa.

Modalities of Treatment

The aim of TRT is to restore the physiological testosterone levels in men with TDS, with the aim of raising serum testosterone levels to the mid normal range. There are several modalities for TRT, and the currently available ones in Singapore are intramuscular injections (short acting or depot), transdermal application of gel and oral preparations. A discussion of the modalities available should be made with the patient, and the appropriate form of treatment can be instituted based on his lifestyle and preference. Each modality has its own advantages and disadvantages, as well as peculiar pharmacokinetics which might affect the testosterone levels in the patients' bodies.

Intramuscular Injection (short acting)

Testosterone cypionate and enanthate has been used historically and widely to help supplement testosterone levels via intramuscular injections of 2-3 weeks intervals.

Short acting injectables may lead to 'peak and trough' effects of testosterone levels, which may be supra-physiological immediately after an injection, thereafter declining over days and weeks, resulting in sub-therapeutic levels just prior to the next injection, with corresponding physiological effects.

Intramuscular Injection (long acting depot)

Long acting depot injection (Testosterone undecanoate) has less 'peak and trough' effects, as the castor oil medium of the preparation helps release the testosterone slowly into the patient's blood stream, resulting in a more stable level of testosterone.

Long acting intramuscular depot injection also has the advantage of being convenient to administer at longer intervals. The initial 2 injections are recommended to be given 6 weeks apart, and subsequent injections at 3 monthly intervals. The intervals can be titrated according to clinical response and testosterone levels.

Long acting intramuscular depot injection has the disadvantage that it cannot be rapidly discontinued. Some patients may complain of local problems at the injection site but this is usually transient.

Transdermal Application of Gel

The skin forms a good absorption medium for testosterone, which bypasses the first pass effect of the liver. It is administered once daily. It is recommended that the gel should be rubbed on the upper arms and abdomen till dry. Hands should be thoroughly washed after application and skin contact of gel application areas with females and children should be avoided 4 hours after the application of the gel. The patient should also avoid swimming within 4 hours after the application of the gel.

Transdermal gel has the advantage of being short acting and can be rapidly discontinued. Some patients might complain of local skin reactions with the gel application.

Oral Capsules

Testosterone undecanoate is the only available safe oral preparation. It is in capsule form, and is absorbed from the intestine via the lymphatic system. Otherwise, if it is absorbed in the blood through the portal system, the testosterone would go through the liver and be degraded there (first pass effect), rendering it inactive.

As a result, testosterone levels may fluctuate with the absorption of the testosterone with the variable amount of dietary fat. However, it has the advantage that it is short acting and can be rapidly discontinued.

Older oral preparations of 17-alkylated androgen such as 17-methyl testosterone must not be prescribed because of their potential liver toxicity.

MONITORING AND SURVEILLANCE

In order to institute TRT safely, initial investigations need to be performed to exclude contraindications to TRT. Follow up investigations serve to assess the efficacy of TRT, and to ensure no adverse effects arise from treatment.

Initial Investigation

Recommended initial investigations are the following:

Prostate Specific Antigen (PSA)
Full Blood Count (FBC)

Optional investigations:

Liver Function Test (LFT)
Fasting lipids

Follow up Investigation

The first follow up investigation can be performed 3 to 6 month after the initiation of TRT. Thereafter, the follow up investigations can be done 3 to 6 monthly. Once noted to be stable, investigations should be performed at least yearly.

Recommended follow up investigations are:

Prostate Specific Antigen (PSA)
Full Blood Count (FBC)

Optional investigations

Liver Function Test (LFT)
Fasting lipids

Digital rectal examination should be performed at least once a year.

The efficacy of the treatment can be monitored through assessment of symptomatic improvement. Appropriate instruments for the assessment should be used, depending on the symptoms that the patient has TRT for. If the patient has erectile dysfunction, IIEF (International Index of Erectile Function) score can

be used to assess his erectile function. If the patient has TRT for osteoporosis, bone densitometry can be performed during initial as well as follow up investigation. Improvement of symptoms from TRT should be sought within a reasonable time interval. Generally, 3 to 6 months is adequate for sexual and psychological functions. If there is a lack of symptomatic improvement, adequacy of TRT should be checked by performing a serum testosterone level. In a study by Mulligan[44], it has been found that 39% of the study population had sub therapeutic testosterone levels (<10.41 nmol/l, 300 ng/dl). If a patient has been given TRT at maximum dosage, and yet fail to achieve therapeutic testosterone levels, then switching to a different agent may help since some patients will absorb one preparation better than another[45].

APPENDIX I

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:	1 none	2 mild	3 moderate	4 severe	5 extremely severe
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)	☐	☐	☐	☐	☐

	1 none	2 mild	3 moderate	4 severe	5 extremely severe
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)	☐	☐	☐	☐	☐

APPENDIX II

Saint Louis University ADAM Questionnaire

1. Do you have a decrease in libido (sex drive)?

2. Do you have a lack of energy?

3. Do you have a decrease in strength and/or endurance?

4. Have you lost height?

5. Have you noticed a decreased "enjoyment of life"?

6. Are you sad and/or grumpy?

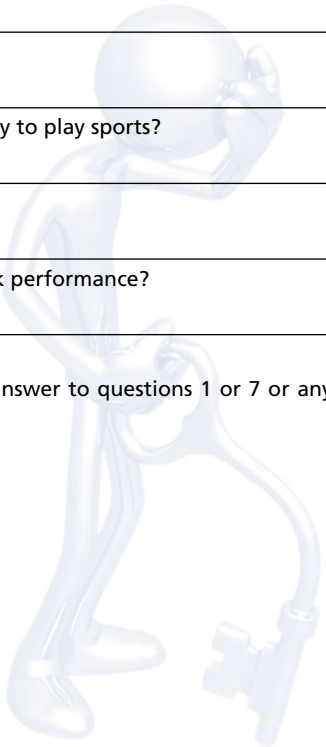
7. Are your erections less strong?

8. Have you noted a recent deterioration in your ability to play sports?

9. Are you falling asleep after dinner?

10. Has there been a recent deterioration in your work performance?

A positive questionnaire result is defined as a "yes" answer to questions 1 or 7 or any 3 other questions.



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