ANDROGEN DEFICIENCY AND LATE ONSET OF HYPOGONADISM

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LATE ONSET OF HYPOGONADISM

- Definition: The syndrome is variously known as andropause, androgen decline in the aging male (ADAM), late-onset hypogonadism (LOH), testosterone deficiency syndrome (TDS)

- It may affect the function of multiple organ systems and result in a significant detriment in the quality of life.

ETIOLOGY AND PATHOPHYSIOLOGY

1. Primary testicular failure is the most frequent cause of hypogonadism and results in low testosterone levels, impairment of spermatogenesis, and elevated gonadotrophins

2. Hypothalamus and pituitary (secondary hypogonadism); central defects of the hypothalamus or pituitary cause secondary testicular failure,

3. Combined primary and secondary testicular failure results in low testosterone level and variable gonadotrophins levels,

4. Androgen target organs (androgen insensitivity or resistance)

- Medication adverse effect
  - Opioid drugs, including methadone and tramadol
  - Long-term glucocorticoid therapy can also suppress the hypothalamic-pituitary-testicular axis.
  - Some drugs used to treat anxiety and depression, either directly or through their provocation of hyperprolactinaemia

Transient testosterone deficiency condition

- Acute illness like head trauma, stroke, myocardial infarction, gall bladder surgery, or acute colitis can also reduce testosterone synthesis.
- Acute severe burns can result in lower testosterone levels
  - *Arch Intern Med.* 2006;166:1660–1665.

PREVALENCE

- Massachusetts Male Aging Study, after the age of 40, the average age-related reduction in total testosterone is 0.8~1.6% per year, whereas free testosterone declines with age by 1.7~2.8% per year
- The incidence of low testosterone and symptoms of hypogonadism in men aged 40-79 years varies from 2% to 6%
- Hypogonadism is more prevalent in older men, in obesity, in those with co-morbidities, and in men with a poor health status

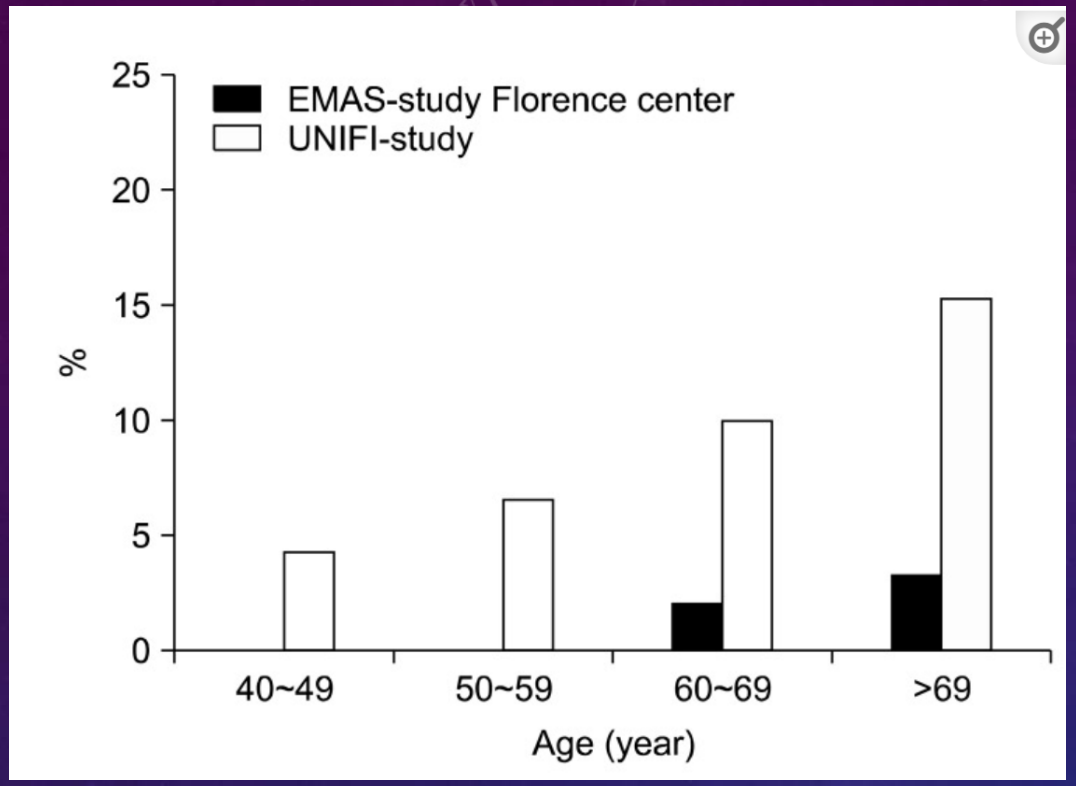
- 1. *J Clin Endocrinol Metab.* 2008;93:3870–3877
- 2. *J Clin Endocrinol Metab.* 2008;93:2737–2745.
- 3. *Int J Clin Pract.* 2006;60:762–769.

- A population-based sample of 6296 men aged 40 years-79 years old was enrolled from six representative provinces in China.
- The overall estimated prevalence of LOH was 7.8% (395/5078)
- 26.1% (103/395) and 73.9% (292/395) had primary and secondary hypogonadism

- Asian J Androl. 2021 Mar-Apr;23(2):170-177.

Risk factors associated with primary and secondary hypogonadism

Parameter	*Primary HG*		*Secondary HG*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
Age (year)	1.152 (1.122–1.183)	<0.001	1.073 (1.059–1.087)	<0.001
BMI (kg m^{-2})	NS	NS	1.123 (1.053–1.199)	<0.001
One or more comorbidities[a]	1.603 (1.049–2.449)	0.029	1.463 (1.143–1.873)	0.003



- Prevalence of hypogonadism according to the European Male Aging Study (EMAS) criteria (13) in Florentine subjects of the EMAS study (n=433) and in a consecutive series of (n=3,293) output-patients attending medical care for sexual dysfunction between 2000~2011 at our center (UNIFI study) .

- **Best Pract Res Clin Endocrinol Metab**. 2013 Aug;27(4):557-79

SYMPTOMS AND SIGNS THAT MAY BE ASSOCIATED WITH FUNCTIONAL HYPOGONADISM

- Specific symptoms
  - Reduced libido
  - Decreased spontaneous erections
  - Erectile dysfunction
- Less specific symptoms
  - Decreased energy
  - Decreased physical strength/function/activity
  - Decreased motivation
  - Low mood
  - Decreased concentration
  - Hot flushes

- Less specific signs
  - Loss of body/facial hair
  - Decreased testicular volume
  - Increased body fat/reduced muscle mass
  - Osteoporosis/low bone density
  - Central obesity

Clinical Manifestations of Late-Onset Hypogonadism and Their Anticipated Response to Treatment

SYSTEM/FUNCTION	AGING	RESPONSE TO TESTOSTERONE
Erectile function	↓	↑
Sexual desire	↓	↑
Mood/cognition	→/↓	↑*
Tiredness/lack of motivation	↓	↑
Sleep disturbances	→/↓	→
Spatial cognition	↓	↑*
Vasomotor (hot flashes)	↑	↓
Quality of life	↓	↑
Hematocrit	↓	↑
Leptin production	↑	↓
LDL and HDL cholesterol	→	↓
Fat mass	↑	↓
Muscle mass	↓	↑
Bone mass	↓	↑
Hair and skin changes	↓	→

- Multivariable-adjusted risk of mortality was twofold higher in those with testosterone level less than 2.5 ng/ml (irrespective of symptoms; HR 2.3; 95% CI: 1.2-4.2) and threefold higher in those with three sexual symptoms (irrespective of serum testosterone; compared with asymptomatic men; HR 3.2; 95% CI: 1.8-5.8).
- Similar risks were observed for cardiovascular mortality.
- A strong correlation between decreased testosterone levels and increased cardiovascular mortality has been reported in meta-analyses
    - *J Clin Endocrinol Metab.* 2014;99:1357–1366.

SCREENING QUESTIONNAIRES FOR TDS

- Three questionnaires
  - (1) St. Louis University's ADAM, (sensitivity and specificity of 88% and 60%)
  - (2) the Aging Male Survey (AMS), (sensitivity 83% and specificity 39%)
  - (3) the MMAS (sensitivity of 60% and a specificity of 59%.)

The Androgen Deficiency in Aging Male (ADAM) Questionnaire

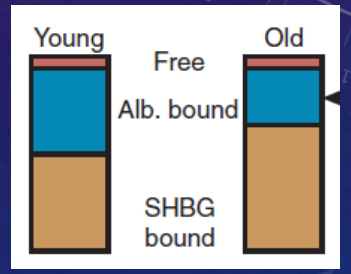
Yes	No	1. *Do you have a decrease in libido (sex drive)?*
Yes	No	2. *Do you have a lack of energy?*
Yes	No	3. *Do you have a decrease in strength and/or endurance?*
Yes	No	4. *Have you lost height?*
Yes	No	5. *Have you noticed a decreased enjoyment of life?*
Yes	No	6. *Are you sad and/or grumpy?*
Yes	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?*

If you answered Yes to questions 1 or 7 or any 3 other questions, you may be experiencing androgen deficiency (low testosterone level).

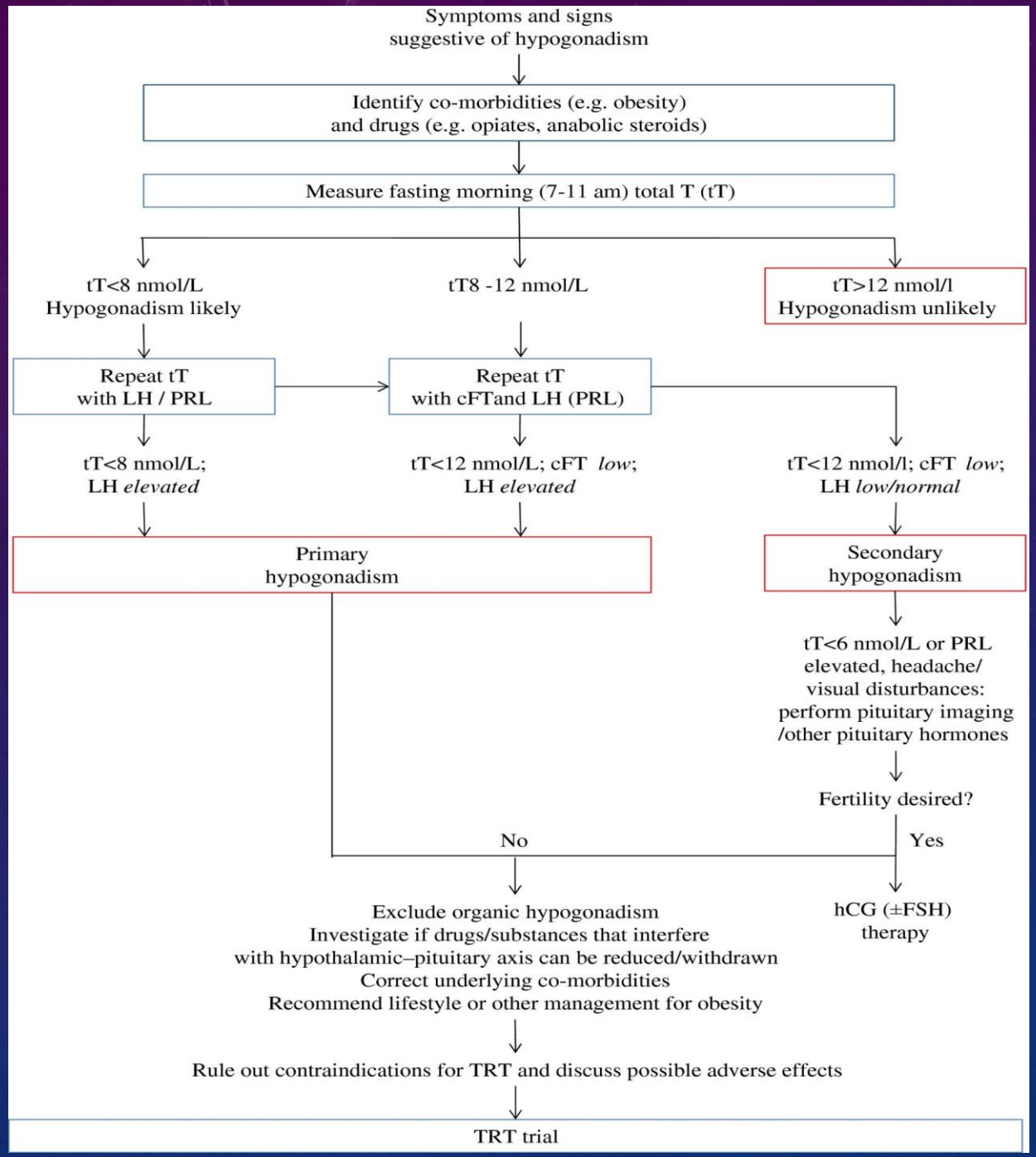
1. 您是否有性慾(性衝動)降低的現象？
2. 您是否覺得比較沒有元氣(活力)？
3. 您是否有體力變差或耐受力下降的現象？
4. 您的身高是否有變矮？
5. 您是否覺得生活變得比較沒樂趣？
6. 您是否覺得悲傷或沮喪？
7. 您的勃起功能是否較不堅挺？
8. 您是否覺得運動能力變差？
9. 您是否在晚餐後會打瞌睡？
10. 您是否有工作表現不佳的現象？

BIOCHEMICAL DIAGNOSIS

- In young men, about 60% of circulating T is bound to sex hormone-binding globulin(SHBG), **38% is bound to albumin, and 1% to 2% is free**.



- **Assays for Testosterone**
  - blood taken between 7:00 and 11:00 AM
  - Men with T levels below 8 nmol/L (230 ng/dL) is definitely
  - **Values between 250 and 360 ng/dL (9 to 12 nmol/L) are considered "borderline." In the presence of a clear picture of TDS, a therapeutic trial of 3 months is justified**


Symptoms and signs suggestive of hypogonadism
Identify co-morbidities (e.g. obesity) and drugs (e.g. opiates, anabolic steroids)
Measure fasting morning (7-11 am) total T (tT)
tT<8 nmol/L Hypogonadism likely
tT8 -12 nmol/L
tT>12 nmol/l Hypogonadism unlikely
Repeat tT with LH / PRL
Repeat tT with cFTand LH (PRL)
tT<8 nmol/L; LH elevated
tT<12 nmol/L; cFT low; LH elevated
tT<12 nmol/l; cFT low; LH low/normal
Primary hypogonadism
Secondary hypogonadism
tT<6 nmol/L or PRL elevated, headache/ visual disturbances: perform pituitary imaging /other pituitary hormones
Fertility desired?
No
Yes
Exclude organic hypogonadism
Investigate if drugs/substances that interfere with hypothalamic–pituitary axis can be reduced/withdrawn
Correct underlying co-morbidities
Recommend lifestyle or other management for obesity
hCG (±FSH) therapy
Rule out contraindications for TRT and discuss possible adverse effects
TRT trial

CONDITIONS THAT MAY ALTER SERUM SHBG AND THEREBY TOTAL T CONCENTRATIONS

- Increased SHBG concentrations
  - Ageing
  - AIDS/HIV disease
  - Cirrhosis and hepatitis
  - Hyperthyroidism
  - Anticonvulsants
  - Oestrogens
  - Polymorphisms in the *SHBG* gene

OPTIONS FOR TREATMENT WITH TESTOSTERONE

Most Frequently Used Testosterone Preparations

	GENERIC NAME	TRADE NAME	DOSE	COMMENTS
Injectable	Testosterone cypionate	Depo-Testosterone cypionate	200-400 mg q 3-4 wk	Supraphysiologic levels Roller-coaster effect
	Testosterone enanthate	Delatestryl	200-400 mg q 4 wk	Same as cypionate
	Testosterone undecanoate*	Nebido	700-1000 mg q 12-14 wk*	Stable levels; unavailable in North America
Oral/buccal	Buccal tabs	Striant	30 mg bid	Inconvenient
	Methyltestosterone†	Metandren	10-30 mg/day	Liver toxicity
	Testosterone undecanoate	Andriol	120-160 mg/day	Not available in United States
		Testocaps		
Transdermal	Testosterone patch	Androderm	5 mg/day	Skin reactions Visible
		Testoderm	10-15 mg/day	Skin reactions
	Testosterone gel	Androgel/Testim	5-10 g/day	Good tolerability. Reproduces circadian rhythm. Variable sites for application.
		Axiron (axillary application)	30-90 mg/day	
		Fortesta (thigh application)	40 mg/day	

*Requires a loading dose of 3 × 1000 mg every 6 weeks for naive patients or of 2 × 1000 mg every 8 weeks for those switching from a different testosterone formulation.
†As 17α-alkylated testosterone products, both fluoxymesterone and methyltestosterone are associated with potential for serious liver toxicity.


Androgel
GEL IN SACHET/GEL IN SACHET
50 mg
Androgel
Androgel
Androgel
Androgel
Androgel
50 mg


4 mg
ANDRODERM
Rx only
Watson

- Natesto (Testosterone Nasal Gel)
- 2014 FDA approval

表. 男性睪固酮藥物補充方式

類　型	說　明
一、肌肉注射劑 (又分成長效型和短效型)	長效型：三個月施打一次，價格較昂貴， 短效型：兩-四週施打一次，價格較便宜； 注射時皮膚局部疼痛、血液中的睪固酮過高時，可能導致紅血球增多症。
二、睪固酮凝膠 (短效型皮膚凝膠擦劑)	每天洗澡後塗抹一次，經由皮膚吸收，使用便利，適合不敢打針的病人；但是會有局部皮膚刺激反應，也可能因接觸而使藥物轉移到婦女或幼童體內。
三、新型鼻內凝膠劑型	按壓噴入鼻腔內，經過鼻黏膜吸收來提高吸收率，方便攜帶、使用便利、操作方便、給藥不沾手、鼻黏膜吸收快。 較不適合鼻子疾病或過敏之族群

TESTOSTERONE REPLACEMENT THERAPY IN THE AGING MALE, AND ITS POTENTIAL BENEFITS

Potential benefits of the testosterone replacement therapy	Administration of testosterone replacement therapy
Effects on body	
Improvement in muscular mass Decrease in fatty mass Increase in muscular strength in lean or moderately fat elderly men Probably a little benefit in lumbar spine bone mineral density	In individuals with low-trauma fractures or osteoporosis, evaluate bone mineral densities of lumbar spine, femur neck, and pelvis 1–2 years after the treatment
Sexual function	
A favourable effect on sexual life in patients with lower pretreatment testosterone levels	Assessments at the beginning, and at 3., and 6. months of the treatment, then annually Also evaluate its effect on erectile dysfunction

Potential benefits of the testosterone replacement therapy	Administration of testosterone replacement therapy
Mood state, and quality of life	
A favourable effect on mood state in patients with lower pretreatment testosterone levels A significant impact on libido could not be found	Assessments at the beginning, and 3., and 6. months of the treatment, then annually
Components of type 2 diabetes mellitus, and metabolic syndrome	
A minor positive effect on HbA1c, and insulin resistance (a few number of findings in favour of contrary opinions have been also asserted)	Lack of any specific recommendations

TURK J UROL. 2014 SEP; 40(3): 170–179.

EUROPEAN ACADEMY OF ANDROLOGY (EAA) GUIDELINES ON INVESTIGATION, TREATMENT

- Lifestyle changes, including physical exercise and weight reduction, in overweight and obese men with functional hypogonadism since weight loss may increase T concentrations
- Transdermal T, as the preferred preparation in the initiation of TRT for functional hypogonadism
- Assess the clinical response as well as adverse effects to TRT at 3 and 12 months after initiation of treatment. Thereafter, clinical review should be scheduled at least yearly

- On-treatment serum total T concentrations should be measured at each clinic visit to ensure that average total T concentrations achieve the targeted
- Digital rectal examination and checking PSA at 3 to 12 months for men >40 years of age after initiating T treatment.
- measuring the haematocrit (Hct) 3-6 months after initiation of TRT and then annually. If Hct is >54%, TRT should be discontinued

Urological consultation if there is:

- (a) an increase in serum PSA concentration > 1.4 ng/mL within 12 months of initiating T treatment,
- (b) a confirmed PSA > 4 ng/ml at any time and
- (c) detection of a prostatic abnormality on DRE
- (d) substantial worsening of LUTS

MONITORING:

- Red blood, DRE and PSA after 6 and 12 months.
- Thereafter: yearly.
- Failure to benefit should result in discontinuation.

CONTRAINDICATIONS

- Prostate and breast cancer
- Elevated haematocrit
- Severe chronic heart failure
- Severe lower urinary tract symptoms (LUTS)/AUA/IPSS > 19)
- Obstructive sleep apnoea
- Active desire to have children

CONCLUSIONS

- Evidence-based data have confirmed the close association between LOH and relevant sexual symptoms, including ED and low libido.
- LOH is frequently comorbid with almost all severe and/or chronic diseases.
- Evidence suggests that TRT is able to improve central obesity (subjects with MetS) and glycometabolic control (patients with MetS and T2DM), as well as to increase lean body mass (HIV, COPD), along with insulin resistance (MetS) and peripheral oxygenation (CKD)

THANK YOU FOR YOUR ATTENTION