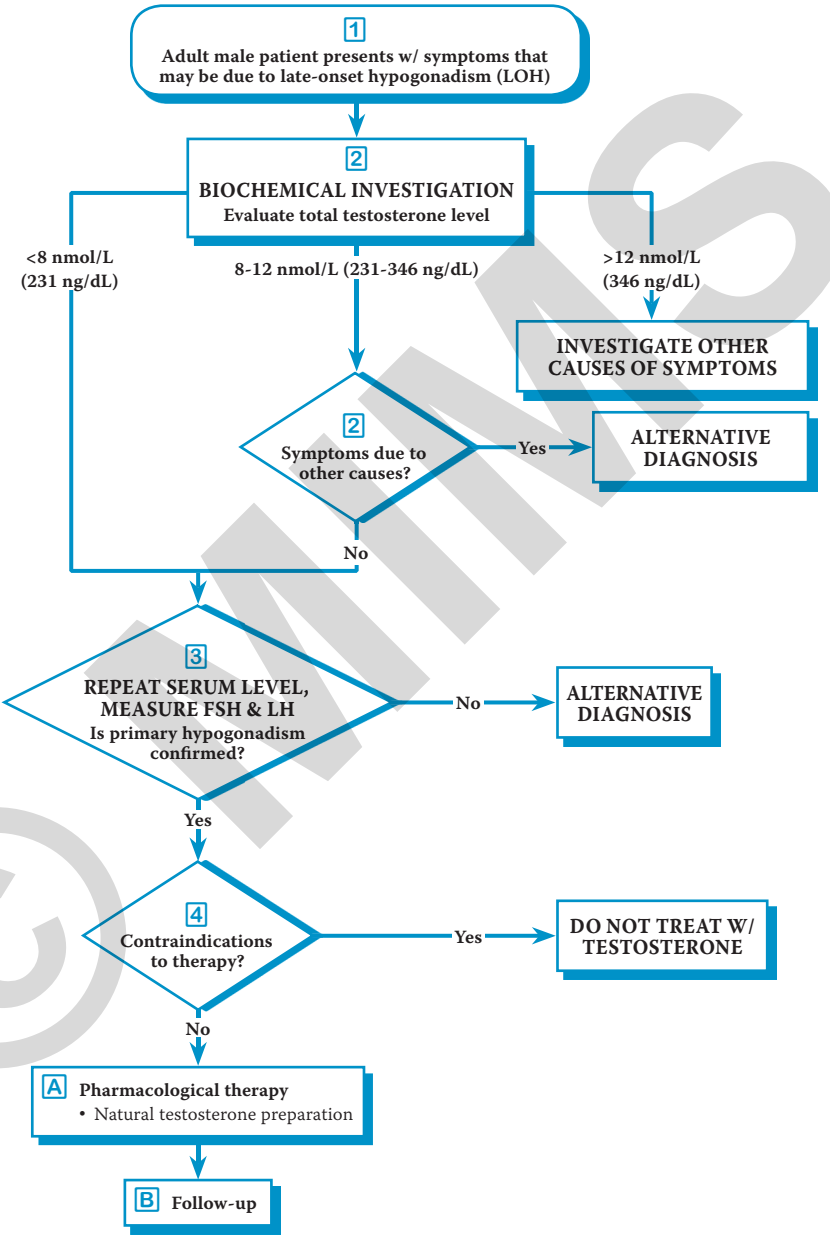
Hypogonadism in Males - Late-Onset (1 of 5)



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1 LATE-ONSET HYPOGONADISM (LOH)

Definition

- LOH is defined as a clinical & biochemical syndrome caused by androgen deficiency characterized by:
  - Older age
  - Set of typical symptoms
  - Deficiency in serum testosterone levels
- A type of hypogonadism that has normal pubertal development thus w/ developed normal male secondary sex characteristics
- Prevalence of hypogonadism increases w/ age
- Quality of life may be decreased
- Multiple organ systems may be adversely affected

Symptoms

- Decreased sexual desire & erectile quality & frequency
- Mood changes, including:
  - Decreases in intellectual activity, cognitive function, spatial orientation ability
  - Fatigue
  - Depression
  - Irritability
- Sleep disturbances
- Decrease in lean body mass w/ decrease in muscle volume & strength
- Increase in visceral fat
- Decrease in body hair & skin alterations
- Osteopenia, osteoporosis & increased risk of bone fractures may develop from a decrease in bone mineral density
- Hot flushes

2 BIOCHEMICAL INVESTIGATION

NOTE:

- ***Serum testosterone level should be obtained between 07:00-11:00 am***
- ***Total testosterone level should be compared w/ the normal ranges established by each laboratory***

Testosterone Serum Level

Normal Serum Testosterone

- There are no specific lower limits of normal serum testosterone in older men
- It is generally agreed that total testosterone level >12 nmol/L (345 ng/dL) do not require testosterone substitution

Low Level

- Based on measurements taken in younger men, if total testosterone level is <8 nmol/L (231 ng/dL) then testosterone substitution should be considered

Low-Low/Normal Level

- In patients w/ the following, testosterone substitution may be considered:
  - Total testosterone level between 8-12 nmol/L (231-345 ng/dL)

  AND
  - Presence of above symptoms that are not due to other causes

Other Investigations

- Full medical history should be undertaken including:
  - Investigation for diabetes mellitus (DM), hypertension, smoking, heart disease, sleep apnea
  - Medication history (eg use of opioids or high-dose glucocorticoid therapy)
- Measure body weight, HR, BP, check CBC, urinalysis & blood chemistry parameters
- Lipid profile & liver function tests are also recommended to assess the patient's risk status
- Assessment of androgen deficient related physical manifestations should be noted
- Questionnaires may be used to evaluate climacteric symptoms, the patient's well-being & sexual function
- Prostate evaluation should be done including measurement of prostate-specific antigen (PSA) & digital rectal exam (DRE)

3 REPEAT TESTOSTERONE SERUM LEVEL & MEASURE FSH & LH LEVELS

- If testosterone level is low or at the lower limit of normal, the level should be repeated for confirmation
- Follicle stimulating hormone (FSH) & luteinizing hormone (LH) levels should also be measured

Primary Hypogonadism (Testicular Origin)

- Low testosterone level w/ increased FSH & LH suggest a testicular failure origin for hypogonadism

Secondary Hypogonadism (Hypothalamic-Pituitary Origin)

- Low testosterone level w/ decreased FSH & LH is suggestive of a hypothalamic-pituitary origin of disease
- Further endocrinological work-up may be needed

4 CONTRAINDICATIONS TO TESTOSTERONE ADMINISTRATION

- Suspected or confirmed carcinoma of the prostate or breast is an absolute contraindication to testosterone replacement
  - Suspected are those w/ palpable prostate nodule or induration or PSA of >4 ng/mL or PSA 3 ng/mL in men at high risk of prostate cancer (eg African Americans or men w/ first-degree relatives w/ prostate cancer)
- Testosterone substitution should be avoided in men w/ significant polycythemia, untreated sleep apnea, severe heart failure, uncontrolled cardiovascular disease, male infertility, hematocrit >0.54%, severe lower urinary tract symptoms due to benign prostatic hyperplasia or significant bladder outlet obstruction

A PHARMACOLOGICAL THERAPY

Principles of Therapy

- Prior to the start of testosterone substitution, there should be confirmation of low serum testosterone & a confirmation of need based on clinical findings
- Only if the potential benefit exceeds the risk, then replacement testosterone should be started
- During HRT, serum testosterone level should be close to normal throughout the day & should ideally follow the normal diurnal pattern
- It is recommended that a baseline DRE & PSA level be obtained before starting testosterone therapy

Natural Testosterone Preparations

- Only preparations of natural testosterone should be used
- 17-α-alkylated androgen preparations are not recommended
  - These can cause poor androgen effects, adverse lipid changes, & hepatic side effects
- There is not enough evidence of benefit to recommend DHT, DHEA, DHEA-S, hCG, androstenediol or androstenedione in older men w/ hypogonadism

Product Selection

- Some authorities recommend the use of short-acting preparations of testosterone so that if a complication develops, rapid discontinuation can be achieved
- Oral, parenteral, transdermal gel & implantable preparations of testosterone are available in Southeast Asia (transdermal patches are available elsewhere)
- Product selection should be agreed upon between the clinician & patient prior to the start of therapy
- Testosterone undecanoate is the most widely used & safest oral mode of administration
  - Rarely causes increase in testosterone levels above the mid-range
  - Oral preparation resorption of testosterone is influenced by intake of fatty food
- A long-acting IM inj testosterone undecanoate is also available given in intervals of 3 months
  - Ensures normal testosterone serum concentration for the entire 3 month period
- Testosterone cypionate & enanthate are available as short-acting IM w/ intervals of 2-3 weeks
  - May cause fluctuations in serum testosterone from high levels to subnormal levels
- Transdermal testosterone preparations are available as skin patches or gel
  - Provides uniform & normal serum testosterone level for 24 hours
  - Gel have advantages of less incidence of skin irritation compared w/ the patch, invisibility of application & flexibility of dosing
  - Gel has the risk of interpersonal transfer (eg to partner or another person who is in close contact)
- Testosterone being applied topically in the axillae has been found to be safe & effective in multinational open-label clinical study & approved in United States & Europe
- Sublingual & buccal testosterone tablets are effective & well-tolerated delivery systems that can provide a rapid & uniform achievement of physiological testosterone level w/ daily administration
- Subdermal depots need to be implanted every 5-7 months & offer a long period of action w/o significant serum fluctuation of the testosterone level
  - There is a risk of infections & extrusions

Potential Benefits of Therapy

Effects on Body Composition

- Androgen supplementation in elderly men has been shown to moderately increase muscle mass
- Fat mass may be modestly decreased
- Reports of increase in strength have been inconsistent
  - Testosterone treatment seems to improve perception of physical function

Skeletal Effects

- Bone mineral density has been shown to increase
  - The lower the pre-treatment testosterone, the greater effect testosterone treatment seems to have on bone mineral density
- Reports of treatment effects on biochemical markers of bone turnover have been inconsistent

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A PHARMACOLOGICAL THERAPY (CONT'D)

Potential Benefits of Therapy (Cont'd)

Libido & Erectile Function

- Testosterone appears to have a moderate to large favorable effect on libido
- Testosterone use in elderly men may have a minimal to small favorable effect on erectile dysfunction
- As some men w/ erectile dysfunction & low serum testosterone levels may not respond adequately to testosterone, addition of a phosphodiesterase-5 inhibitor may be indicated

Cognition

- There are limited observations of beneficial effects of testosterone treatment on cognitive function in elderly men

Mood & Quality of Life

- Studies have not shown consistently that there is improvement in mood or quality of life in elderly men treated w/ androgens

Glycemic & Lipid Control

- Studies have shown positive effects on glycemic & lipid control, insulin resistance & visceral adiposity in hypogonadal men w/ impaired glucose tolerance & lipid profiles
  - Thus, there is a consequent decrease in the cardiovascular risk

Adverse Effects

Prostate

- It is not known if testosterone supplementation in the older male promotes the development or acceleration of prostate cancer
- Testosterone supplementation in older men seems to induce only a small increase in the volume of the prostate w/ an eventual moderate increase in the prostate specific antigen (PSA) level

Hematology

- Testosterone stimulates erythropoiesis
- A significant rise in blood cell mass & hemoglobin can occur from testosterone therapy in older men
- If the hematocrit rises to >50%, withholding therapy may be indicated or in some cases phlebotomy may be necessary

Obstructive Sleep Apnea

- Evidence are inconsistent correlating testosterone supplementation w/ obstructive sleep apnea

Gynecomastia

- Testosterone may be associated w/ the development of gynecomastia from the aromatization of testosterone to estrogen

Lipid & Cardiovascular Safety

- Data are insufficient to determine whether testosterone supplementation would increase, decrease or have no effect on CV disease

B FOLLOW-UP

- The patient should be monitored carefully (by monthly check-up every 3 months) for the development of adverse effects

At 1 Month & 3 monthly thereafter

- Follow up w/ patients to assess that the desired testosterone level is achieved
  - Optimal serum testosterone level for efficacy is unknown
  - It is generally recommended that mid to lower young adult levels may be appropriate as the therapeutic goal
- Evaluate the patient for complications/adverse effects & determine if symptoms are improving

During 1st Year of Therapy

- Perform prostate exam, PSA, hematocrit every 3 months
  - Hematocrit >54% requires dose reduction or temporary medication discontinuation
  - If the PSA increases >0.75 ng/mL over 2 consecutive controls or a PSA level abnormal for age (>4 ng/mL), further exam & eventual biopsy may be needed
- Plasma lipid determinations at the 3rd & 6th month of therapy
- Liver function test, urinalysis & measurement of bone markers may be done at the 6th month

At 1 Year

- Repeat all previous tests done on the 6th month
- Blood glucose control should be evaluated by fasting blood glucose (FBG), post-prandial glucose (PPG) or HbA_{1c}
- After the 1st year, follow-up may be done every 6 months for 2 years & annually thereafter

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Dosage Guidelines

ANDROGENS & RELATED SYNTHETIC DRUGS		
Drug	**Dosage**	**Remarks**
IM Inj		
Testosterone cypionate 100 mg/mL, 200 mg/mL	50-400 mg IM every 2-4 wk	**Adverse Reactions** • Endocrine effects (gynecomastia, patients w/ BPH may develop urethral obstruction, elderly may have higher risk of developing prostatic hypertrophy, oligospermia w/ prolonged or excessive use); Lipid effects (serum cholesterol may increase); Hematologic effects (increase in Hct, Hgb); CNS effects (headache, anxiety, depression); Dermatologic effects (hirsutism, male pattern baldness, seborrhea, acne); GI effect (nausea); Other effects (edema, fluid & electrolyte disturbances) • Inflammation & pain at site of IM inj **Special Instructions** • Contraindicated in patients w/ prostate or breast cancer • Use w/ extreme caution or not at all in men w/ significant polycythemia, untreated sleep apnea, severe heart failure or significant bladder outlet obstruction • Topical gel is applied on the abdomen or on both inner thighs - Daily rotation between the abdomen & inner thighs is recommended
Testosterone decanoate 100 mg, testosterone isocaproate 60 mg, testosterone phenylpropionate 60 mg,testosterone propionate 30 mg/mL	1 mL IM every 3 wk	
Testosterone enantate (Testosterone enanthate) 250 mg/mL	250 mg IM every 2-3 wk To maintain adequate androgenic effect 250 mg IM every 3-4 wk	
Testosterone undecanoate 1000 mg/4 mL	1000 mg (4 mL) slow IM inj every 10-14 wk (1st inj interval may be reduced to min of 6 wk)	
Implant		
Testosterone 100 mg/implant, 200 mg/implant	100-600 mg implanted SC every 4-5 mth	
Oral		
Mesterolone 25 mg tab	25 mg PO 8 hrly **Maintenance dose:** 25 mg PO 12-24 hrly	
Testosterone undecanoate 40 mg cap	**Initial dose:** 120-160 mg/day PO divided 12 hrly x 2-3 wk **Maintenance dose:** 40-120 mg/day PO divided 12 hrly Should be taken w/ food	
Topical Gel		
Testosterone	Apply 3-5 g 24 hrly in AM **Max dose:** 10 g/day	

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
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Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers' product information.

Specific prescribing information may be found in the latest MIMS.

Please see the end of this section for the reference list.