What is the problem with the ageing person?

What is wrong with getting older and andropausal?
The ageing person, in the process of growing older physiologically, is less functional & is exposed to greater risks of diseases including diabetes and CVDs. The ageing person should be allowed to age gracefully with good quality of life, still enjoy life and relationships including sexual relations.
The ageing person also suffers from decreasing cognition, memory function & mental concentrating ability. Anxiety depression, feelings of being useless, labile moods all increase with increasing age in both men & women.

Barret-Connor et al; The Rancho Benardo Study; J Clin Endocrinol Metab; 1999

MEN’S HEALTH: TESTOSTERONE AND AGEING
In males, these symptoms of labile moods and deteriorating memory are suggestive of male menopause or andropause (LOH) with low testosterone.

The combination of a younger woman and andropausal husband may be a cause of deteriorating relationships.

This can be worsen if there is sexual disorder....
Alternative terms:

- Partial androgen deficiency ageing males.

But this implies loss of androgen and spermatogenesis.
What is the pathophysiology of testosterone or androgen deficiency in ageing men?

Is this usual for all men as they grow older?
- Pituitary
  - Gonad-stimulating cells

- FSH
- LH

Together with testosterone, FSH stimulates spermatogenesis.
LH stimulates testosterone secretion.

- Testosterone
  - Sperm producing cells in testes secrete testosterone.

- Male pattern of development (before birth)
- Enlargement of male sex organs and expression of male secondary sex characteristics (starting at puberty)
- Male behaviour and libido
Male Hypogonadism

Secondary hypogonadism

Primary hypogonadism

Hypogonadism
Hypogonadism

Primary

Congenital
- Klinefelter’s syndrome
- Hemochromatosis
- Anorchia
- Cryptorchidism

Acquired
- Testicular Trauma/Infarction
- Orchitis
- Drugs: chemotherapy

Secondary

Congenital
- Kallman syndrome
- GnRH receptor mutation

Acquired
- Prolactinoma
- Pituitary tumor
- Post radiation

Cause:
Pathophysiology of late-onset hypogonadism

hypothalamic-pituitary-gonadal axis defects

Why and how do we get late onset hypogonadism or andropause?

• Impaired hypothalamic secretory reserve, resulting in a reduced and chaotic secretion of Gonadotrophin Releasing Hormone (GnRH).

• Reduced pituitary response to GnRH, resulting in an increased but irregular LH pulse frequency of reduced amplitude.

• Loss of the circadian rhythm of testosterone production.
Circadian rhythm of serum testosterone is lost in ageing men

![Graph showing the circadian rhythm of serum testosterone in young and old men.](image)
Testosterone levels decline in ageing men
Massachusetts Male Aging Study

- Key findings:
  - Free testosterone declined by 2.8% per year
Serum Concentrations of Total Testosterone (T), Sex Hormone Binding Globulin (SHBG), and Free Testosterone (FT) in Men of Different Ages

Fig. 2. Proportion of men with low total testosterone [<300 ng/dl (10.4 nmol/liter)], low free testosterone [<5 ng/dl (0.17 nmol/liter)], and high SHBG (>46.25 nmol/liter, defined as highest quintile of SHBG) by 10-yr age group. T, Testosterone.
Prevalence of hypogonadism in ageing men
Baltimore Longitudinal Study of Aging

Harman et al. J Clin Endocrinol Metab 2001;86:724-731
MEN’S HEALTH: TESTOSTERONE AND AGEING

Testosterone target organs

- Brain
- Testicles
- Prostate
- Penis
- Cardiovascular system
- Muscle
- Bone
- Liver
- Adrenals
Does this relatively benign testosterone deficiency matter? Are there clinical signs and symptoms of testosterone deficiency?

If substituted, is there a significant clinical improvement of signs and symptoms?

Is it safe?
In 434 male patients aged over 50 years, Zitzmann et al. (JCEM 2006 91:4335) observed an increasing prevalence of symptoms with a decrement of androgen concentrations. The symptoms included:

- Loss of libido: p < 0.001
- Loss of vigour: p < 0.001
- Obesity: p < 0.001
- Feeling depressed: p = 0.001
- Disturbed sleep: p = 0.004
- Lacking concentration: p = 0.002
- Diabetes mellitus type 2: p < 0.001
- Hot flushes: p < 0.001
- Erectile dysfunction: p = 0.003

Patients (n):
- Total testosterone nmol / L:
  - 20: 74
  - 15: 69
  - 12: 84
  - 10: 65
  - 8: 67
  - 0: 75
MEN’S HEALTH: TESTOSTERONE AND AGEING

A  Sexual Symptoms and Total Testosterone

- Decreased frequency of morning erection
- Erectile dysfunction
- Decreased frequency of sexual thoughts

Probability

Total Testosterone (nmol/liter)

- 11 nmol/liter
- 8 nmol/liter
- 8.5 nmol/liter

MEN’S HEALTH: TESTOSTERONE AND AGEING

B Sexual Symptoms and Free Testosterone

- Decreased frequency of morning erection
- Erectile dysfunction
- Decreased frequency of sexual thoughts

Probability

Free Testosterone (pmol/liter)

160 pmol/liter

280 pmol/liter
MEN’S HEALTH: TESTOSTERONE AND AGEING

C  Physical Symptoms and Total Testosterone

- Decreased vigorous activity
- Difficulty walking >1 km
- Decreased bending

![Graph showing physical symptoms and total testosterone](image)

- Probability
- Total Testosterone (nmol/liter)
- 13 nmol/liter

MEN’S HEALTH: TESTOSTERONE AND AGEING

Physical Symptoms and Free Testosterone

- Decreased vigorous activity
- Difficulty walking >1 km
- Decreased bending

Probability vs. Free Testosterone (pmol/liter)

MEN’S HEALTH: TESTOSTERONE AND AGEING
MEN’S HEALTH: TESTOSTERONE AND AGEING

Psychological Symptoms and Free Testosterone

- Fatigue
- Loss of energy
- Sadness

Free Testosterone (pmol/liter)

Probability

160 pmol/liter
Decline in Testosterone Levels is Associated with Comorbid Conditions rather than with Age

Co-Morbidities in Hypogonadal Men

# Odds Ratio of Selected Co-Existing Diseases

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Odds Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>2.33 (1.90, 2.85)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.04 (1.67, 2.50)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.80 (1.50, 2.14)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.59 (0.77, 3.30)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>1.55 (0.91, 2.62)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.49 (1.25, 1.78)</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>1.42 (1.07, 1.88)</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>1.20 (0.95, 1.50)</td>
</tr>
<tr>
<td>Prostate Disease</td>
<td>1.19 (0.95, 1.49)</td>
</tr>
</tbody>
</table>

Waist Circumference and Testosterone Levels in 1,548 Community Dwelling Men (age 25 – 84) - The Tromsø Study -

Waist circumference in cm

References:

Strong association between the METABOLIC SYNDROME (visceral obesity, hypertension, dyslipidemia, insulin resistance, hyperglycemia) and ERECTILE DYSFUNCTION
Proportion of Hypogonadism in 300 Male Patients with Type 2 Diabetes (mean age 58 years)

Insulin sensitivity (M mg/kg\textsuperscript{-1} min\textsuperscript{-1})

R = 0.4

P<0.005

Testosterone nmol/L

5  10  15  20  25  30

Low testosterone levels predict diabetes

Unadjusted Kaplan-Meier Survival Curves for 3 Testosterone Level Groups in 858 Veterans > 40 years

Men, average age 60 years
2x Total-Testosterone > 8.7 nmol/L, n=452
1x Total-Testosterone > 8.7 nmol/L, n=240
2x Total-Testosterone < 8.7 nmol/L, n=160
Late-onset hypogonadism was associated with negative psychosocial and quality of life variables including:

- low physical activity, $p=0.007$
- frequent headaches, $p=0.02$
- feeling very tired, $p=0.045$
- frequent misunderstandings, $p=0.01$
- low sexual interest, $p=0.023$
- psychic vulnerability, $p=0.024$
- abdominal pain, $p=0.0015$
- living alone, $p=0.032$

The most notable but seldom complained about problem of the ageing person is the decline in Sexual Function.

Ageing associated with low testosterone associated with decrease frequency of orgasms, increase in refractory period, decrease in sexual thoughts & enjoyment.
MEN’S HEALTH: TESTOSTERONE AND AGEING

TESTOSTERONE

Sexual Excitement & Libido

Penile tissues

ORGASM

Computer rendering of male genitalia, showing penis, testis, epididymis and vas deferens.
Testosterone levels are decreased in ageing men with erectile dysfunction.

Prevalence of libido problems is increased in ageing men
National Health and Social Life Survey
Low libido in ED?

80% of Viagra non-responders have decreased libido.


Tsujimura et al 2003
Conditions with a High Prevalence of Low Testosterone Levels in which we Suggest Measurement of Serum Testosterone Levels (Endocrine Society Guidelines)

- End-stage renal disease and maintenance hemodialysis
- Moderate to severe chronic obstructive lung disease
- Osteoporosis or low trauma fracture
- Type 2 diabetes mellitus
• Testosterone levels in early morning serum sample;
  • Total Testosterone below 11 nmol/l
  • Free Testosterone below 0.25 nmol/l
  • With normal LH, FSH & Prolactin

Kaufman & Vermeulen, in Neischleg E, Behre HM, Testosterone Ed 2 Springer 1997;
Swerdloff & Christina Wang in The Aging Male 2001

• Serum SHBG if very obese

When is measurement of free or bioavailable Testosterone clinically important?

Important!

NO benefit from free T = sure low

ABNORMAL

Testost  8 12  14 nmol/l

NO benefit from free T = sure normal

NORMAL
What to do when testosterone measurement is ambiguous?

Are the symptoms of late onset hypogonadism very strong and convincing, if yes, prescribe testosterone.

Testosterone measurement: 8-13 nmol/l

- **ABNORMAL**: Below 8 nmol/l
- **NORMAL**: 8-13 nmol/l
QUALITY OF LIFE IN AGEING MALES

TREATMENT

• Androgen therapy for ageing males -
QUALITY OF LIFE IN AGEING MALES

increase muscle bulk and size
increase lean mass
decrease abdominal fat

Testosterone replacement in elderly results in:

- increase muscle bulk and size
- increase lean mass
- decrease abdominal fat

Snyder et al 1999; J. Clin. Endocrinol Metab; 842687
Relationships have many levels

Sexual Function = Power & Self

Erectile function is for the man first, not the relationship

Cultural emphasis towards embarrassment 'Face' (loss)

Sex / ED is not discussed
The partner or husband:

Passive & Unconcerned, so the menopausal sexually non-functional wife is not a problem.

Why treat himself?

The menopausal woman: Willing to accept a life without sex. Thinks that sex is overrated. Feelings may be supported by partner.
Androgen therapy may be given as subcutaneous implants which may last up to 1 month (Sustanon) or 3 months (Nibido), or as oral testosterone undecanoate (40mg; Andriol) capsule or as androgen gel rub onto skin.

Advantage of oral/gel is that it may be ceased at any time.
Major concerns for TESTOSTERONE supplementation?

? 

?
A three-year follow-up of androgen treatment in hypogonadal men

• Long term study: three year follow up

• N=165, age: 19-67

• PSA: increased, but remained in normal range

• Three subjects (1.8%): elevated PSA, and PC

– Similar to background rates of PC
Andriol® and Prostate

- Long term: 10 years Gooren study
  - No liver function impairment
  - No prostate tumour
  - PSA: within normal range

- Prostate data in most recent studies
  - 5 studies since 2000 (n=482):
    - Study length: up to 12 months, dosage: 80mg/day - 80mg tid.
    - No PSA increase
Rhoden & Morgentaler: "There appears to be no compelling evidence at present to suggest that men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgen increases this risk"
Recommendations
(ISSAM and CAS)

- Testosterone Replacement Therapy: symptoms and biochemical evidence

- Contraindication:
  - PC, breast cancer, severe BOO (bladder outlet obstruction)
  - BPH with moderate or no BOO (relative)

- Monitoring:
  - Symptoms, baseline DRE, PSA (>40yr mandatory)
  - Follow up: 3, 6 and 12 month first year, and yearly thereafter
Testosterone and Lipid Profile

• Supraphysiologic, injectable Testosterone: decrease HDL
• Physiologic replacement, HDL: no change or minimal reduction
• Meta-analysis, intramuscular Testosterone ester: neutral on lipid profile (Whitsel et al. 2001)

Conclusion:
Testosterone replacement therapy within the physiologic range is not associated with worsening of the lipid profile
Testosterone Replacement Therapy Monitoring

- Treatment is normally for life.
- Follow-up patients quarterly for the first year to assess clinical & biochemical response (DRE, PSA).
- Patients who remain stable can then be followed annually (also include: hemoglobin, liver function, lipids).
- Clinical response is the most reliable indicator of treatment effectiveness regardless of serum testosterone levels (social behavior, emotional, sense of well-being, energy, etc.).

MEN’S HEALTH:
TESTOSTERONE AND AGEING
Should low testosterone be treated?

YES

Androgen replacement with medications example Andriol or Sustanon is effective and safe.
Andropause should be treated in symptomatic people.