Outline

- Introduction: the topic, what I will cover, my acronym
- Definitions and their problems, ISSAM definition
- Why are we interested
- How does T change as we age?
- How androgens work
- The classification of hypogonadism
- Why does aging lead to loss of androgens?
- Other endocrine changes with aging
- Epidemiology
- Clinical changes seen
- Diagnosis
- The level which defines hypogonadism
- Treatment
- Why is there controversy about Rx
- What are the effects of Rx?
  - Sexual
  - Body composition
  - Cognition
- Who should be treated? (slide 94)
- Criteria for Rx
- Stopping treatment
- Options for delivery
- What are the risks?
  - Prostate
  - CV
  - Other
- Monitoring
- Conclusions

Ageing Associated Androgen Deficiency

AAAD

Rod Studd
Urology Fellow

Who?
How to treat
The Risks
And how to monitor

Andropause

=

Viropause/Male Climacteric/Penopause

=

AAAD

=

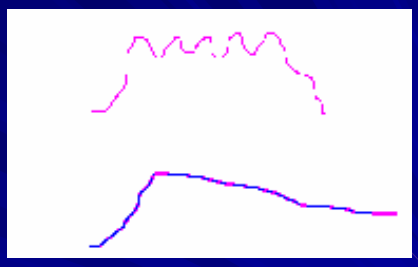
PADAM & ADAM

Andropause – a misnomer

- **Andropause implies cessation of testicular activity**
- It is derived from 'menopause'

  men =month + pauein =to cause to cease

  Where ovarian function ***ceases..***



Andropause vs. Menopause

- Gonadal function in the older male continues if even at a lower level
- Menopause is <u>universal</u> and <u>obvious</u>
- *Andropause is not universal & manifestations often subtle*

International Society for the Study of the Ageing Male Definition:

- ***'A clinical and biochemical syndrome associated with advancing age*** *and characterized by a deficiency in serum androgen levels with or without a decrease in genomic sensitivity to androgens. It may result in significant alterations in the quality of life and adversely affect the function of multiple organ systems'*

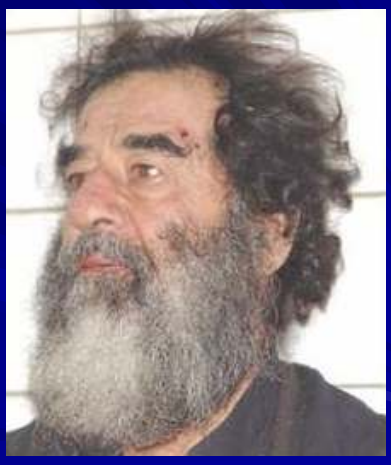
Symptoms are important!

- ADAM is common
- However, symptoms of ADAM are less common

Symptoms are important!

Symptomatic
Androgen
Deficiency of the
Ageing
Male

S ymptomatic
A ndrogen
D eficiency of the
A geing
M ale



Why are we interested ?

- Recent increased medical awareness of AD & consequences in older men
- Patient *demand* for 'vigorous golden years'?
  - Unmet needs of older men?
- Men's health a 'political issue'

Why are we interested ?

- Pharmaceutical industry marketing of new T replacement products, they see $$$$$
  - Manufacturing of a 'disease'?

    Direct to consumer marketing

500% increase in prescription sales of T products since 1993 [(13)]

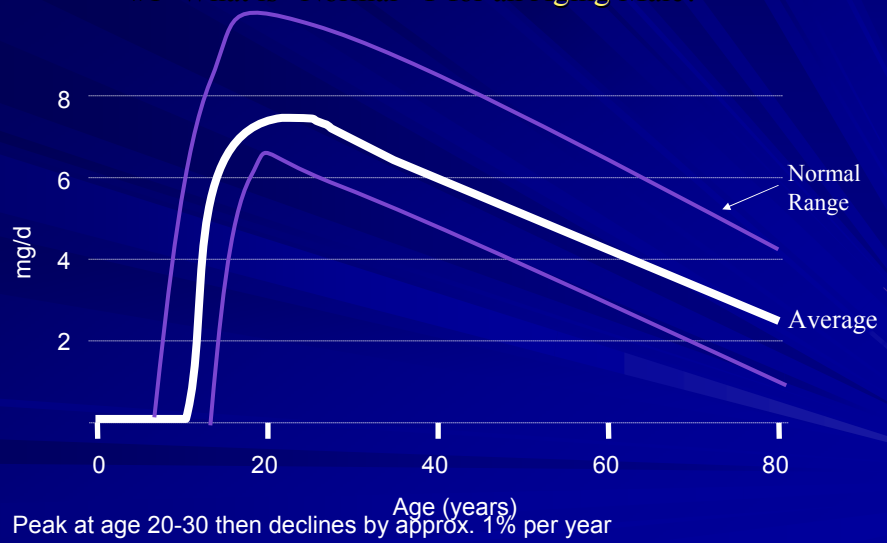
Why is there controversy?

Poorly Defined *Indications* for treatment
Clinical entity poorly defined
Testosterone levels not a good marker

Questionable
benefits of
Treatment.
No rigorous trial of the objective benefits has been performed

Theoretical ***Risks***
Of treatment
NO RCT to evaluate safety of <u>prolonged</u> TRT

Testosterone Production as a Function of Age
but:
#1 What is "Normal" T for an Aging Male?

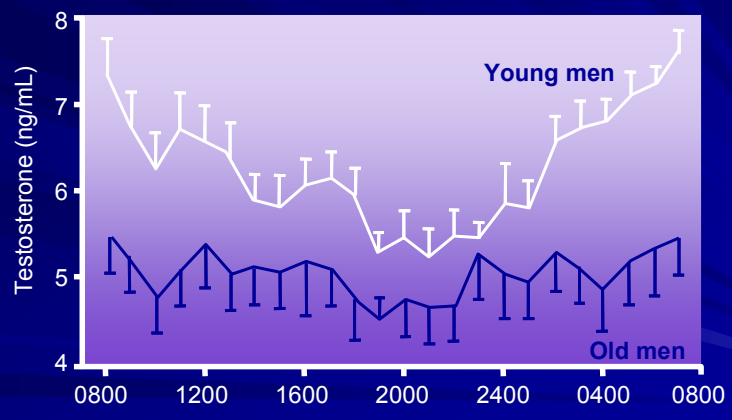


Peak at age 20-30 then declines by approx. 1% per year

Rate of decrease higher in:

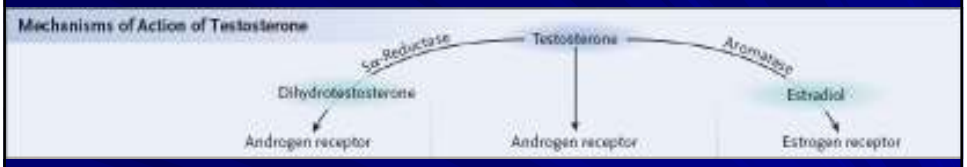
- Obesity
- Diabetes
- Illness, medications

Diurnal rhythm (peaks in AM) dampened in older men



Bremner WJ, et al. *J Clin Endocrinol Metab* 1983

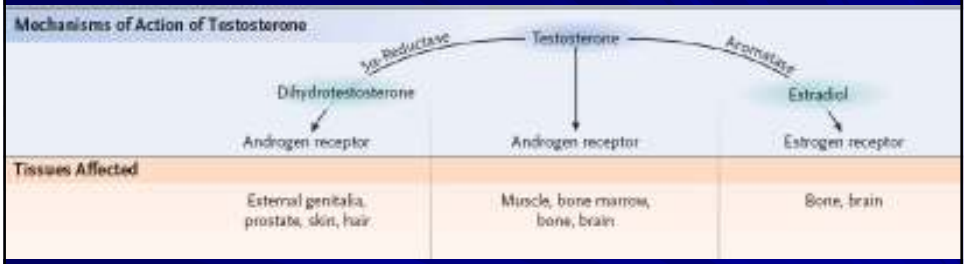
Androgen Physiology



Testosterone can act as three different hormones

N ENGL J MED 350;5 January 2004

Androgen Physiology



Reproductive and *Non-Reproductive* actions

N ENGL J MED 350;5 January 2004

Causes of Hypogonadism

Primary Hypogonadism

Secondary Hypogonadism

Combined hypogonadism

Less severe in degree of hypogonadism than 1 or 2

Serum T and LH levels allow discrimination of causes

Causes of Hypogonadism

1. Primary Hypogonadism

LH

T

Primary = Leydig Cell failure

Klinefelters

Orchitis

Testicular tumours

Maldescended testes

Causes of Hypogonadism
2. Secondary Hypogonadism

Secondary = Hypothalamic or Pituitary Failure

Hypopituitarism

Pit' tumours

Kallmann Syndrome

LH

T

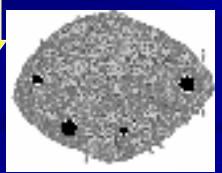
Causes of Hypogonadism
3. Combined Failure

Pituitary Gland

Low LH

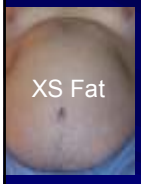
Combined failure
common in older men

Low T



Leydig Cell

How does aging lead to loss of androgens?



XS Fat

Adipokines

Impaired Leydig cell function

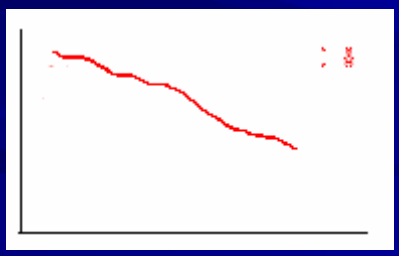
Hypothalamic Function

Sex Hormone Binding Globulin

Decreased Bioavailable Testosterone

What endocrine changes occur as we age?

- Acronyms over-simplify the endocrine changes of ageing – *Androgen deficiency rarely occurs in isolation*
- Several hormones are affected by the aging process:



Production of weak adrenal androgens declines

Decline more predictable and profound than testosterone

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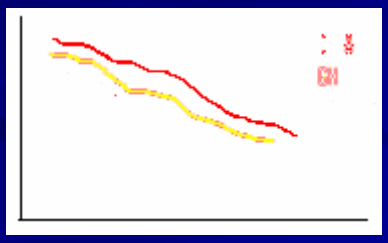


Pituitary Production of GH

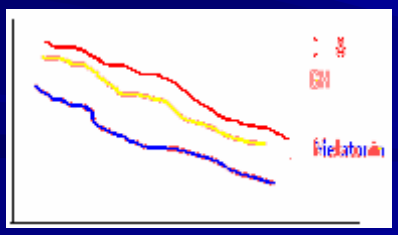
Peaks at puberty

Declines markedly with age

Associated with loss of mass & strength

What endocrine changes occur as we age?

- Acronyms over-simplify the endocrine changes of ageing – *Androgen deficiency rarely occurs in isolation*
- Several hormones are affected by the aging process:



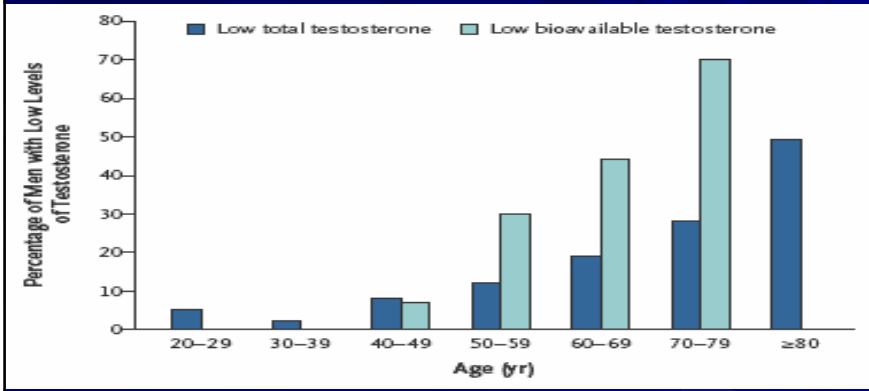
Pineal Gland Production of Melatonin

Decline plays a role in the sleep disturbance seen with aging- often attributed to low T

The Scope of the 'Problem'

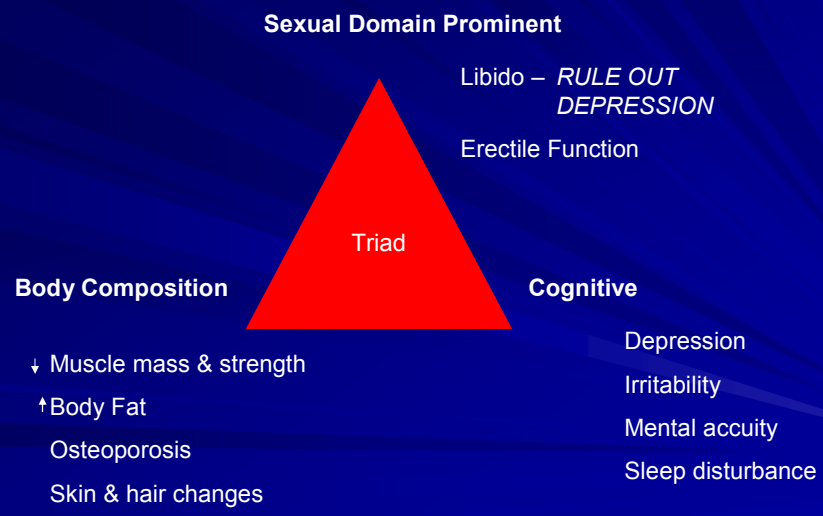
- The world is getting older
  - World popn' doubled 1950-1990
  - Will double again by 2025
  - 1950: <5% age >65yrs
  - 2025: >15% age >65yrs
- **And heavier…**
  - **Higher rates of obesity & diabetes**

Observational Studies - BLSA



- A partial decline in gonadal hormones with age is universal
- 30% of men over age 60 (<11.4ng/dL)
  50% of men over age 70
- However, there is great inter-individual variability in T levels among *healthy* older men

Clinical Manifestations of ADAM



Clinical Diagnosis of ADAM seldom made…

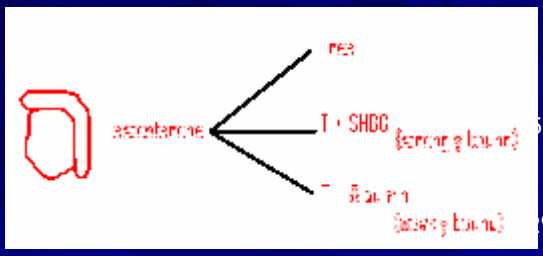
- *Low physician awareness*
- *Signs & symptoms often subtle & only slowly progressive & attributed to ageing or other disease*
- Screening

  Ask about: sexual function, strength,

  Questionnaires available:

  Morley Questionnaire: sens 88%, spec 40%

Biochemical Diagnosis



We need:

A cheap and reliable test which reflects the individual degree of androgenicity

Morning sample: 8:00-11:00am

Subject of much controversy: several measurements and assays

Total T

- Widely available✓
- Automated✓
- Consistent✓
- Easy to perform✓
- Cheap✓

- Good for initial evaluation

However…. If SHBG is elevated total T level does not reflect bioavailable T (ageing & obesity)✗

Free testosterone

- *Should be* the most accurate index of androgenisation

However..Type of assay affects accuracy:

equilibrium dialysis✓
ultracentrifugation✓

Expensive×
Need expertise×
Rarely performed

Radioimmunoassay×

Cheap, automated and notoriously inaccurate

Calculated Free Testosterone

- Complicated formula integrates SHBG and total T levels to give free T

Formula available: www.issam.ch/freetesto.htm

As accurate as free or bioavailable T✓
Cheap ✓

Bioavailable Testosterone

- =Free + Loosely bound T

Not automated✗
Need expertise and experience ✗

Free Androgen Index

$$\frac{\text{Total T}}{\text{SHBG}}$$

Simple✓
Unreliable✗
Not recommended ✗

Recommend

- Bioavailable or Calculated free testosterone
- If T abnormal or at lower limit
  - Repeat the test
  - FSH, LH, TSH & Prolactin

What T level defines Hypogonadism?

Normal range in 20-40 year old men 10.5-35nmol/L

- 10.5nmol/L =2.5SD below the mean level of the male reference popn
- Most experts agree, <7nmol/L is abnormal and >14nmol/L is normal
- *However, a significant proportion of men in the 7-14nmol/Lrange complain and have signs of androgen deficiency*

Are the normal ranges too high ?

Study of 266 healthy men

Hormone	Time	Age	N	Lower	Upper
Testosterone nmol/L	AM	<=40	198	10.07	38.76
		>40	68	7.41	24.13
	PM	<=40	198	6.69	31.51
		>40	49	6.46	21.93

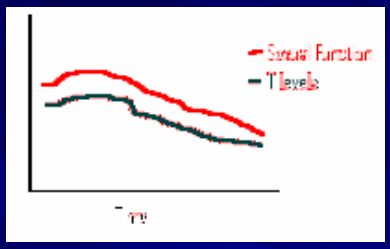
•Published Normal ranges 10 35 nmol/L

"The lower limit of 'normal' in healthy men may be at least 3-4 nmol/L(.86-1.15ug/L) lower than the published ranges, esp for evening samples and for men >40yrs."

Boyce et al BJU 2004

What are the beneficial effects of treatment?

1. TRT and Sexual Function



Sufficient testosterone levels are required for:

- Libido
- Erection
- Ejaculation

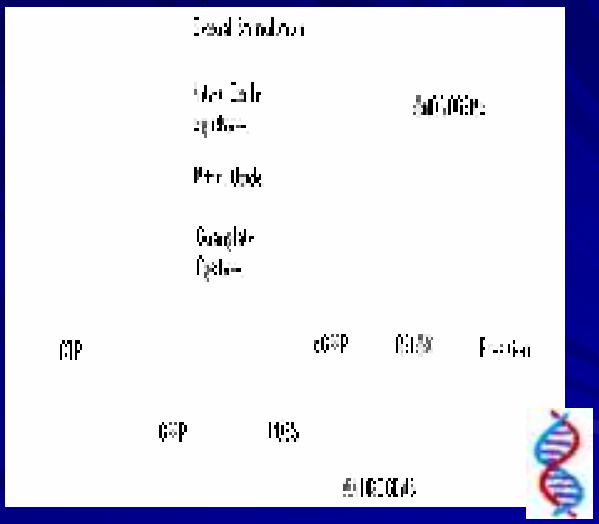
Normal Erectile Function

Endogenous vasoconstrictors

Endogenous vasodilators

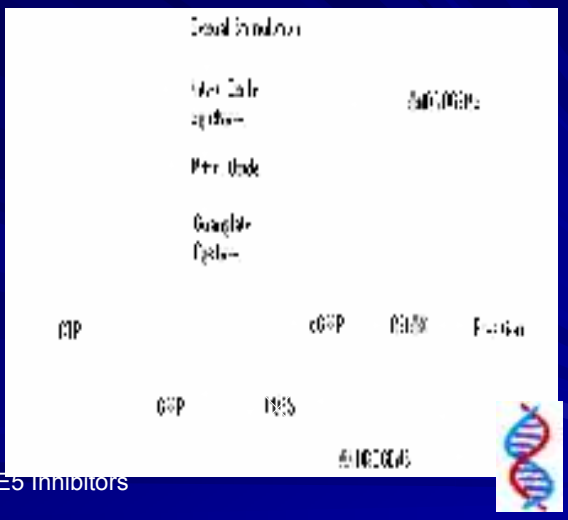
A balance

How do low T levels impact on erectile function?



Androgens regulate expression of neuronal NOS and function of the PDE5 gene

Recent studies show that PDE5I's plus Testosterone improve erectile ability in hypogonadal men



PDE5 Inhibitors

Meta-analysis of 17 RCT's of TRT and Sexual Function (Isidori et al)

- Meta-analysis valuable because many reports have low power
  - Median study length only 3 months (1-36)
  - 656 subjects

Results:

- Effects on erectile function were inversely related to mean baseline T level
- TRT did not improve erectile function in eugonadal men
- If T <3.4ng/L at baseline; TRT improved:
  - Nocturnal erections
  - Sexual thoughts and motivation
  - Number of successful intercourses
  - Scores of erectile function
  - Overall sexual satisfaction
- The T threshold for the behavioural components of sexual function (libido) was lower than for the erectile function domain
- Most of the improvement is seen in the first few months then the benefits plateau off and decline over time

Conclusions:

- TRT may be beneficial for sexual function in men with low T levels
- TRT may be useful in restoring erectile function in men failing PDE5 inhibitors with low T levels

2.TRT and Body Composition

Does TRTimprove body composition?

- Meta-analysis of RCT's (Isidori et al)
- 29RCTs
- 1083 men, Mean age 64.5yrs
- Mean T:10.9nmol/L

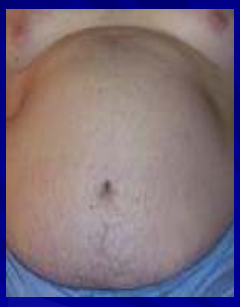
Total Body Fat Reduction

- Reduction of 1.6kg (CI:2.5-0.6); -6.2% after average of 9 months of treatment
- Mainly abdominal fat

Is this *clinically meaningful?*

An increase in intra-abdominal fat is associated with greater mortality for cardiovascular events

?Will TRT therefore improve cardiovascular risk, No data, therefore Cannot recommend TRT for weight control……yet



Muscle

- Increase in muscle mass of 1.6kg (CI:.6-2.6); +2.7%
- Less clear cut effects on muscle strength:
  - Muscle strength: only dominant knee extension and handgrip showed a tendency towards improvement over placebo

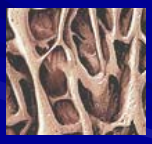
Bone Mineral Density

- Androgens act on bone via aromatisation to oestrogens

TRT and Bone Mineral Density

Metaanalysis

- Increased BMD
  - @ L spine of 3.7% after a minimum of 12-36 months
  - No change at femoral neck
  - BMD continues to increase after 30 months of Rx
- Bone resorption markers decrease
- *No clear evidence of reduction in falls & fractures*



Which men are in need of treatment?

Which men are in need of treatment?

Symptomatic men with a *low testosterone*

Analogy: BPH

Several Criteria need to be met before prescribing treatment

1. Symptoms *and* biochemical support for the diagnosis
2. Absence of contra-indications:
   - *Significant obstructive symptoms*
   - *Suspected or documented CaP or Ca breast*
   - *Severe sleep apnoea, Hct >50%, Severe CHF*
3. Expert follow-up and a motivated patient

This approach should minimize risk and improve QOL in the treated group

Are there alternatives to TRT?

- Exercise
- Diet
- Education

Can improve ‘body composition’ and cognitive + sexual domains without the need for drugs

How to treat?

- Delivery?
- Dose?
- Target Testosterone levels?
- Dose adjustment?
- Monitoring of side effects?

Baseline Evaluation

LUTS & Sleep Apnea History
DRE
PSA
Hb
Lipids
Screen for DM

Delivery

Oral

T. Undecanoate

(Not methylated forms)

Intramuscular T esters

T. enanthate

Patches

Testosterone

Gels

Testosterone

Each system has its advantages & disadvantages

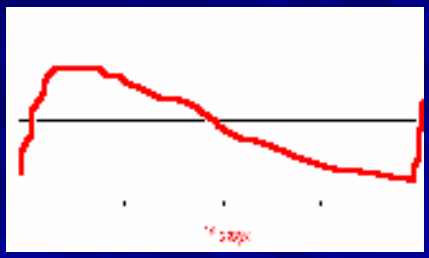
In terms of clinical endpoints, no study has shown significant differences

Choice of delivery often comes down to practicalities

IM Testosterone enanthate (Delatestryl)

- 250mg every 18-28 days
- Supraphysiologic serum levels occur 2-5 days after injection

"The Roller coaster"



Advantages Low cost, high peak T levels, Decades of experience has proven its safety

Disadvantages Pain, Frequent visits, "Roller coaster" of symptoms
Higher risk of polycythaemia

IM Testosterone Undecanoate 1000mg

- A new agent
- Depot injection lasting for 3 months
- No “Roller Coaster” phenomenon

Oral Testosterone Undecanoate (Andriol)

Chylomicrons pass through intestinal lymphatics & thoracic duct

- *This avoids the first pass effect*
- Daily dose can be adjusted to circadian rhythm

Several Problems:

TDS dosing after a fatty meal
Bioavailability is erratic
GI intolerance

Not first choice of Rx

Transdermal Patches (Androderm)

Scrotal patch the original..
- Daily application
- Good serum testosterone levels achieved
- Required shaving of scrotal skin

Non-Scrotal Patches
- Absorption enhancer made this possible
- Skin reactions in >60%

Testosterone Gel 1% (Androgel)

- Hydroalcoholic Gel 5-10g (50-100mg T.)
- Daily application to shoulders and abdomen , 5 min to dry

- Advantages:
  - Ease of use,
  - Levels return to baseline within 3-4 days once Rx stopped
  - Reduced skin reaction (66% of patch users & only 5%of Gel users)
  - Long term data(>3yr) available for gels

- Cons:
  - Agent can be passed on to partner
  - Expensive

Goals of Therapy

- Biochemical normalisation and symptom improvement
- 3 month trials are useful in determining efficacy and suitability of longer treatment

Dosing

- Most studies of TRT achieved levels T during Rx >14nmol/ (median of young men)
- Thus, if adequate levels are not achieved, the subjective benefits reported in the trials may not be seen
- Dose required for *Perceived benefit* depends on the starting T level:

Severe Hypogonadism (<7nmol/L)

- Perceived benefits occur at a lower dose

So

Aim for a lower target level of 10nmol/L

Mild Hypogonadism

- Waste of time/money to raise T to 10nmol/L

So

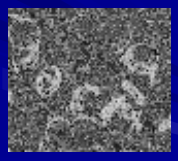
Aim for a higher target level of 15-20nmol/L

When should Rx stop?

- Androgen deficiency does not resolve
- Treatment of a partial deficiency reduces endogenous production
- Most experts recommend treatment for life
- If treatment does not provide benefits or causes problems then stop

What are the risks of TRT?

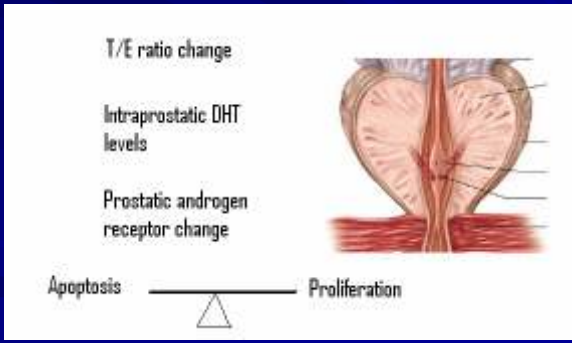
What are the risks of TRT?



- *A RCT to evaluate safety of prolonged TRT is not available*

Testosterone and BPH

- BPH is clearly related to ageing
  - –prostate growth of 2% per year (Olmsted County Study)
- Due to:



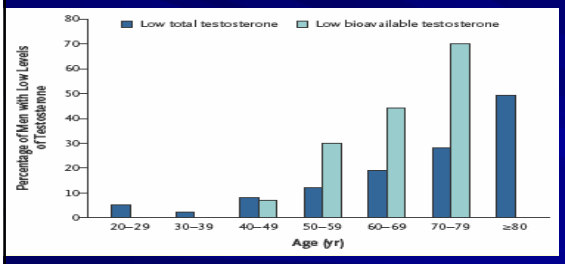
TRT and BPH

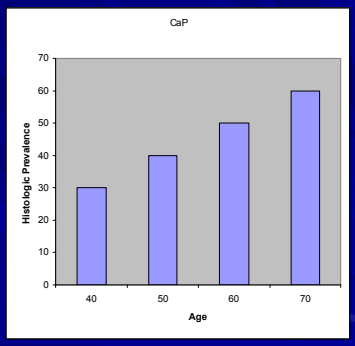
- In hypogonadal men
  - *Prostate volume increases mainly during the first 6 months of therapy to a level equal to that of eugonadal men*
- Multiple Studies have shown no change in:
  - *Symptom scores*
  - *Maximum Flow Rates*
  - *Rates of urinary retention*
  - – On an individual basis, TRT may cause increased voiding symptoms

TRT contra-indicated if bladder outflow obstruction or severe LUTS

Prostate Cancer & Ageing

Testosterone deficiency, like prostate cancer is more prevalent in older populations..





TRT and Prostate Cancer

60 years ago Huggins showed that suppression of testosterone causes regression of prostate cancer….

Does elevating Testosterone cause prostate cancer to appear?

Endogenous hormone levels & CaP

Massachusetts Male Aging Study

Prospective, population based study of aging in 1576 men 40-70 years old (8 year follow up)

- 4% developed CaP
- 17 hormones (androgens, estrogens, adrenal & pituitary hormones) assessed for CaP risk

No association of T level and CaP risk

Only one hormone, (Androstanediol) was associated with CaP risk

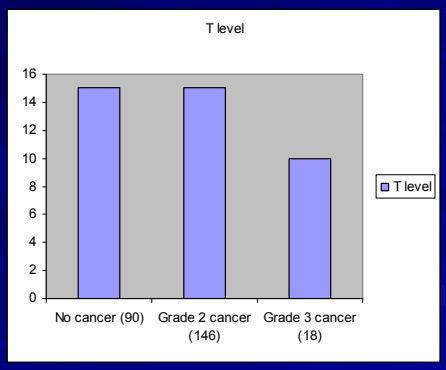
- Non-linear & inverse relationship..?significance

Frozen sera studies :no difference in T levels between men in whom prostate cancer developed 7-25 years later and those in whom it did not

Prostate Cancer may suppress Serum T ..

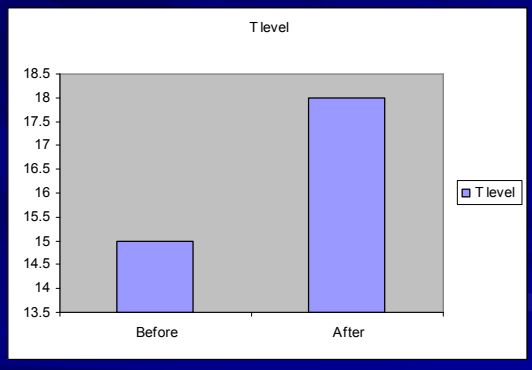
Zhang et al assayed Testosterone levels prior to biopsy (*Prostate*, 2002)

Levels of T in men with and without Cancer



Zhang et al, Prostate 2002;53:179

Levels of T following prostatectomy (n=79)



Zhang et al, Prostate 2002;53:179

Is Occult Prostate Cancer more prevalent in hypogonadal men?

Increased Rate of Occult CaP in hypogonadal men?

Low Testosterone levels

Suppressed PSA levels

Prostate Cancer in Hypogonadal men

- Biopsy of 77 hypogonadal men with normal PSA & DRE's
- *14% had CaP*
- *Higher than the expected rate in men with normal DRE and PSA*

Morgentaler et al. JAMA, 1996

TRT and PSA

•T trials have *inconsistently* shown a rise in PSA- the mean increase has been 0.3-0.43ng/mL

Study	Duration	Increase in PSA	
		Placebo	Testosterone
	mo		*number/t*
Hajjar et al. (1997)[32]	24	–	–
Sih et al. (1997)[9]	12	0/15	0/17
Dobs et al. (1999)[11]	24	–	1/33
		–	0/33
Snyder et al. (1999)[8]	36	7/54	13/54
Snyder et al. (2000)[6]	36	–	–
Wang et al. (2000)[20]	6	–	0/76
		–	1/73
		–	4/78
Kenny et al. (2001)[7]	12	3/33	8/34

If a rise occurs, it occurs in the first 6 months & remains stable thereafter

Managing PSA in men on TRT

•Several Approaches have been Published:

•Biopsy **all** before commencing TRT

•Biopsy only if PSA increases by >1 in first 6 months of Rx (Bhasin et al)

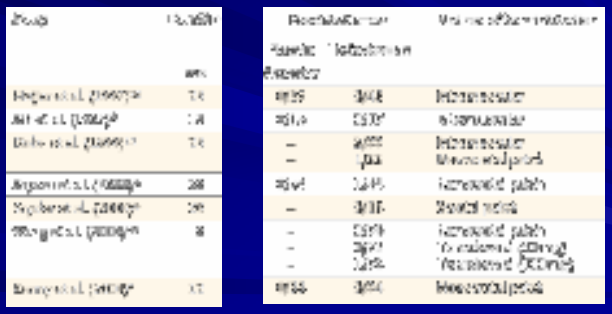
•Biopsy only if PSA velocity >0.75ng/mL/yr or if age specific ranges are exceeded (Endocrine society)

There is no credible evidence that prostate biopsies are indicated prior to TRT

Can TRT convert an occult CaP to a clinically apparent tumour?

Several anecdotal reports

7 Published prospective studies..



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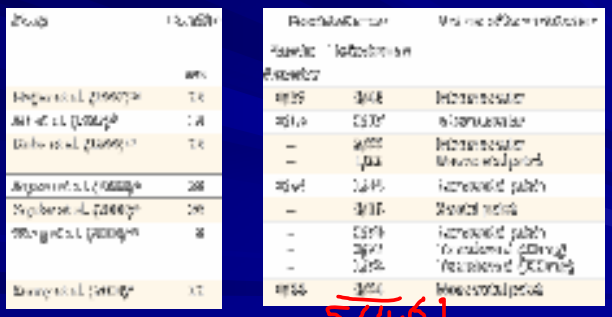


1.1% over 6-36 months: a prevalence rate similar to general population rate

BUT… only 36 months of follow up.

Is TRT ‘Safe’ in men ‘Cured’ of CaP?

Scarce data..

	# pts	Months from RP	Followup (months)	PSA Recurrence
Kaufman J Urol 2004	7	32 (0-108)	41 (12-144)	0
Agarwal J Urol 2005	10	?	19	0

Post Radiotherapy
Is persistent disease a concern ?

- EBRT Monotherapy
  Biopsy:persistence of CaP in 14-91%
- + Adjuvant AD
  Biopsy:<5% rate of CaP persistence

Post Surgery

- Pathological examination of the specimen and more definitive interpretation of post-treatment PSA levels allows more precise prognostication & assessment of residual disease
- *More confidence in prescribing TRT*

In the absence of data, recommend..

- Consider primary therapy modality & balance the risks of disease recurrence & progression vs. QOL benefits.
- After successful Rx of CaP, ART may be prescribed after a prudent interval
- Avoid supraphysiologic levels
- Monitor closely

Cardiovascular Disease

Is T a risk factor for CVD?

Few, if any data support a causal relation between higher T levels and heart disease

Coronary Atherosclerosis & T levels:

no relationship Kabakci at al 1999

CAD associated with lower levels of T then men without CAD English et al 2000

Aortic Atherosclerosis & T levels

Population based Rotterdam Study 2002 (504 men)

Men with higher T levels had lower relative risks of aortic atherosclerosis.

TRT may have a *favourable* effect on risk of CVD

T replacement in Angina patients RCT of 46 men

Men with stable angina treated with transdermal TRT had greater angina-free exercise tolerance than placebo English 2000:Ref 23

Intracoronary injections of testosterone

Injection of physiologic doses lead to increase in mean coronary diameter & blood flow

Effect on Haemostasis and Thrombosis of supraphysiological doses

32 men treated for 1 year with IM Testosterone.

Supra-physiological doses of T did not affect platelet activity

No overall change in thrombotic risk

TRT studies

Rates of AMI, CVA,& angina unchanged

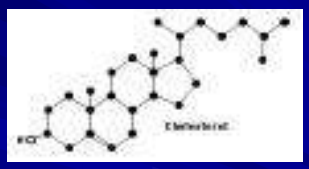
But…

Long term data on CV risk is not available

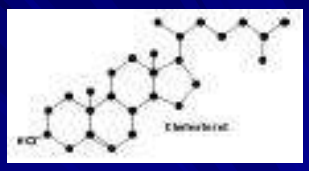
Need large, prospective RCT's

TRT and Serum Lipids

- Data are controversial



The Theory…



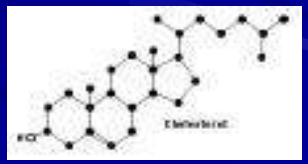
Exogenous T → ↑ Lipoprotein lipase → ↓ HDL

↓

INCREASED CARDIOVASCULAR RISK

Meta-analysis shows:

- Reduction in total cholesterol by .23mmol/l
  - Effects more pronounced in hypogonadal men
- No change in LDL
- Small HDL *reduction*
  - -0.085mmol/l *in men with higher baseline T levels*



Polycythaemia

Hypogonadal men have lower Hb levels

Higher T levels stimulate RBC Production

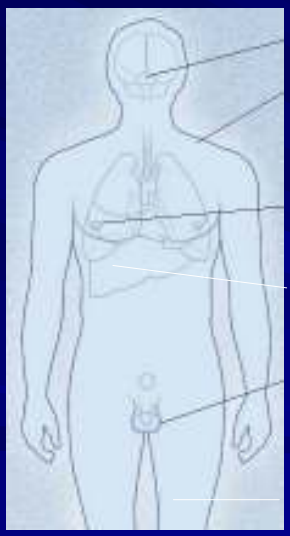
Association with: *Supra-physiological* levels of T

Delivery mode

Author	Mode of Delivery	Rate of Erythrocytosis
Dobs et al (ref 27)	Patch	15.4%
	IM	*43.8%*
Snyder et al (ref 28)	Patch	5.5%
Wang at al (ref 29)	Patch 5mg	2.8%
	Gel 5mg per day	11.3%
	Gel 10mg per day	17.9%

Dose reduction, or phlebotomy may be required

Other Sites of Potential Risk



Sleep Apnea via central mechanisms: *infrequent*

Skin: Acne, oily skin, increased hair, flushing: *All infrequent*

Local reactions to topical agents

Breast: Gynaecomastia: *Infrequent*

Liver: Limited to oral agents, monitoring of LFT's unnecessary with transdermal agents

Testes: Atrophy and infertility: Common

Fluid Retention: *uncommon & usually mild*

Monitoring During Therapy

- Early in Rx

1-2 month visit:

T levels and assess clinical response. May need to adjust dose

3-6 month visits for 1 year then annually

Check clinical response, LUTS, sleep apnea, DRE, T level , PSA, Hb

Can we learn *anything* from the HRT experience?

The Similarities of TRT now to HRT in the 1990's are Thought Provoking..

Stated benefits of TRT in Male → Improved sexual function

Improved body composition

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Very similar to…..

Stated benefits of HRT in women *before* long term follow up was available → Reduction of menopausal symptoms

Cognitive, Sexual, Bone and CV benefits

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Stated benefits of TRT in Male → Improved sexual function; Improved body composition

Stated benefits of HRT in women *before* long term follow up was available → Reduction of menopausal symptoms; Cognitive, Sexual, Bone and CV benefits

in a milieu of:

high consumer interest

Industry promotion $$

And *hormone sensitive glands with high background rates of cancer in the population*

What happened to HRT?

Womens Health Initiative

- 16,000 patient placebo controlled randomized trial

Results:

Reduced risk of fractures and reduced menopausal symptoms

However.

- *Estrogen + Progestin resulted in:* ***Increased*** *risk of MI, Stroke, blood clots,* ***Invasive breast cancer*** *and dementia*

!

Now, FDA recommends

- Use of HRT only if at significant risk of osteoporosis and alternative Rx's fail
- Use the *lowest* dose and *shortest* duration of treatment that is effective

What does the WHI experience mean to men?

- Extrapolation of this study to men is inappropriate;
  - *Different* gender
  - *Different* hormones
  - *Different* end-organs (breast, heart)

However, the WHI should be a cautionary tale for urologists…

..Avoid indiscriminate use of testosterone and monitor your patients on TRT

The Safety Study that needs to be done:

- WHI sized safety studies have not been done in men
- To evaluate prostate cancer risk, >5000 men and >5year follow-up is needed
- Until the study is done, cautious treatment of symptomatic men is indicated

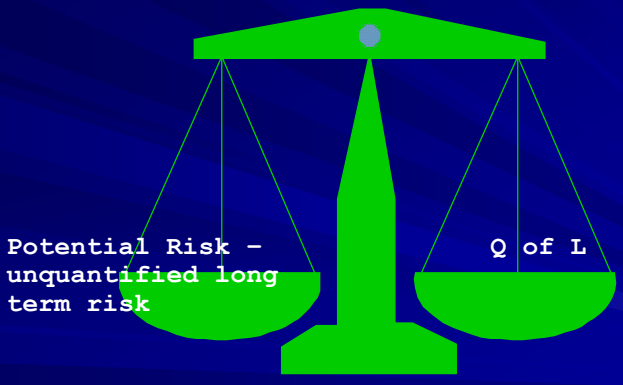
Summary

- ADAM is a defined, non life threatening condition
- Age associated changes are not due solely to low T
- Biochemical confirmation & DRE + PSA mandatory before initiating therapy
- New mechanisms of delivery
- Risks are recognized and can probably be reduced by follow up
- Prospective randomized clinical trials are needed to evaluate long term risk

Until the evidence comes in..

Until the evidence comes in..

Try to balance the Equation



- **Informed decision making**