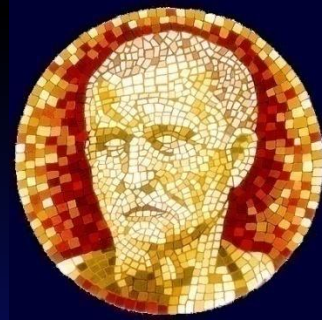




**Bar-Ilan University  
Faculty of Life Science  
Israel**

**International Society  
for the Study of the  
Aging Male (ISSAM)**



**ISA, ISSAM, EAU, EAA and ASA  
recommendations: investigation,  
treatment and monitoring of late-onset  
hypogonadism in males**

**Prof. B. Lunenfeld MD PhD**

8th European Congress on Menopause, May 16 –20, 2009 in London, UK,

# Introduction

- Demographic data clearly demonstrate that the percent of population in the older age group is increasing.
- Androgen deficiency in the aging male has become a topic of increasing interest and debate throughout the world.
- Cross-sectional and longitudinal data indicate that testosterone falls progressively with age and that a significant percentage of men over the age of 60 years have serum testosterone levels that are below the lower limits of young adult men
- The principal questions raised by these observations are whether older hypogonadal men will benefit from testosterone treatment and what will be the risks associated with such intervention.

# Benefit of androgen treatment of hypogonadal men

- The past decade has brought evidence of benefit of androgen treatment of hypogonadal men on multiple target organs and recent studies show short-term beneficial effects of testosterone in older men that are similar to those in younger men.
- This has been comprehensively reviewed and summarized by the Institute of Medicine in “Testosterone and Aging: Clinical Research Direction”.

# T\* equally efficacious in younger and older men

•Age	19 - 59	yrs	60-68
•n	119		52
•LBM	+ 4.5%	n.s	+ 3.9%
•fat	- 5.4%	n.s.	- 4.4%

Swerdloff et al 2002

# Process for development of recommendations

- The revised recommendations are supported by a selection of appropriate references and categorized by the level of evidence and grade of recommendation according to the US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research (1992).

# Recommendation 1:

## Definition

- Late-onset hypogonadism (LOH, also referred to as age-associated testosterone deficiency syndrome, TDS) is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels (below the young healthy adult male reference range).
- This condition may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems.

# Recommendation 2 .1

## Clinical Diagnosis and Questionnaires

- At present, the diagnosis of treatable hypogonadism requires the presence of symptoms and signs suggestive of testosterone deficiency (Level 3, Grade A).
- The symptom most associated with hypogonadism is low libido, other manifestations of hypogonadism include: erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality and depressed mood.
- None of these symptoms are specific to the low androgen state but may raise suspicion of testosterone deficiency.
- One or more of these symptoms must be corroborated with a low serum testosterone level (Level 3, Grade A)

# Recommendation 3.1: Laboratory Diagnosis

- In patients at risk or suspected of hypogonadism a thorough physical and biochemical work-up is necessary (Level 4, Grade A).
- Transient decreases of serum testosterone levels such as due to acute illnesses should be excluded by careful clinical evaluations and repeated hormone measurement.
- Hypogonadism (primary or secondary) can occur at all ages including elderly men.

# Recommendation 3.1

## Risk factors for hypogonadism in older men

- Risk factors for hypogonadism in older men may include chronic illnesses including diabetes mellitus, chronic obstructive lung disease, inflammatory arthritic, renal and HIV-related diseases, obesity, metabolic syndrome and hemachromatosis.
- Such chronic diseases should be investigated and treated (Level 4, Grade A).

# Meta-Analysis of Testosterone (T) Levels & Type 2 Diabetes in 6,427 Men

- **Cross-sectional Studies (n=36):**

T levels are lower in men with T2DM than controls,, \ P<0.001

- **Prospective Studies (n=7):**

Men with higher T levels (450-600 ng/dL) had a 42% lower risk of developing T2DM than those in the lower dichotomy (RR 0.58 [0.39-0.87])

# Recommendation 3.2: Laboratory Diagnosis

- A serum sample for total testosterone determination should be obtained between 07.00 and 11.00 h (Level 2a, A).
- The most widely accepted parameters to establish the presence of hypogonadism is the measurement of serum total testosterone.
- There are no generally accepted lower limits of normal. There is, however, a general agreement that total testosterone level above 12 nmol/L (350 ng/dL) does not require substitution. (Level 2b, Grade A).

# Recommendation 3.2: Laboratory Diagnosis

- Similarly, based on the data of younger men, there is consensus that patients with serum total testosterone levels below 8 nmol/L (230 ng/dL) will usually benefit from testosterone treatment.
- If the serum total testosterone level is between 8 and 12 nmol/L, repeating the measurement of total testosterone with sex hormone binding globulin to calculate free testosterone may be helpful .(Level 2b, Grade A).

# Diagnosis & Treatment of LOH Patient Selection Algorithm

Clinical symptoms of late-onset hypogonadism

Total testosterone (TT) & SHBG (7 – 11 am)

Low: TT <8nmol/l

Borderline: TT = 8-12nmol/l

Normal: TT >12nmol/l

Repeated measurement  
TT + LH, FSH, PRL,  
Validation of low T  
or low free T

Calculate free T\*

No androgen deficiency  
Seek other causes

Elevated LH, FSH

Low or low normal LH,  
FSH, or PRL elevated

Low free T  
<225 pmol/l

Normal free T  
>225pmol/l

Exclusion of  
contraindicatio  
ns

Evaluation of pituitary  
and hypothalamic  
function

*Trial of  
testosterone*

Treatment of the disease,  
*Trial of testosterone*

\*www.issam.ch

LH = Lutenizing hormone  
FSH = Follicle stimulating hormone  
PRL = Prolactin  
SHBG = Sex hormone binding globulin

Nieschlag E, Swerdloff R et al. *Int J Androl.* 2005; 28:125-127.  
Lunenfeld B, Saad F et al. *Aging Male.* 2005; 8:59-74.

Close monitoring  
validation of clinical  
improvement

# Recommendation 3.9

## Laboratory Diagnosis

- Alterations in other endocrine systems occur in association with aging (i.e. estradiol, GH and DHEA) but the significance of these changes is not well understood.
- Determinations of estradiol, thyroid hormones, cortisol, DHEA, DHEA-S, melatonin, GH and IGF-I are not indicated unless other endocrine disorders are suspected based on the clinical signs and symptoms of the patient (Level 2, Grade A).

# Recommendation 4:

## Assessment Of Treatment Outcome And Decisions On Continued Therapy

- Improvement in signs and symptoms of testosterone deficiency should be sought.
- Failure to benefit clinical manifestations within a reasonable time interval should result in discontinuation of treatment (3–6 months is adequate for libido and sexual function, muscle function, and improved body fat).
- Improvement in bone mineral density requires a longer interval to show improvement) Failure to benefit should result in discontinuation of treatment.
- Further investigation for other causes of symptoms is then mandatory (Level 1b, Grade A).

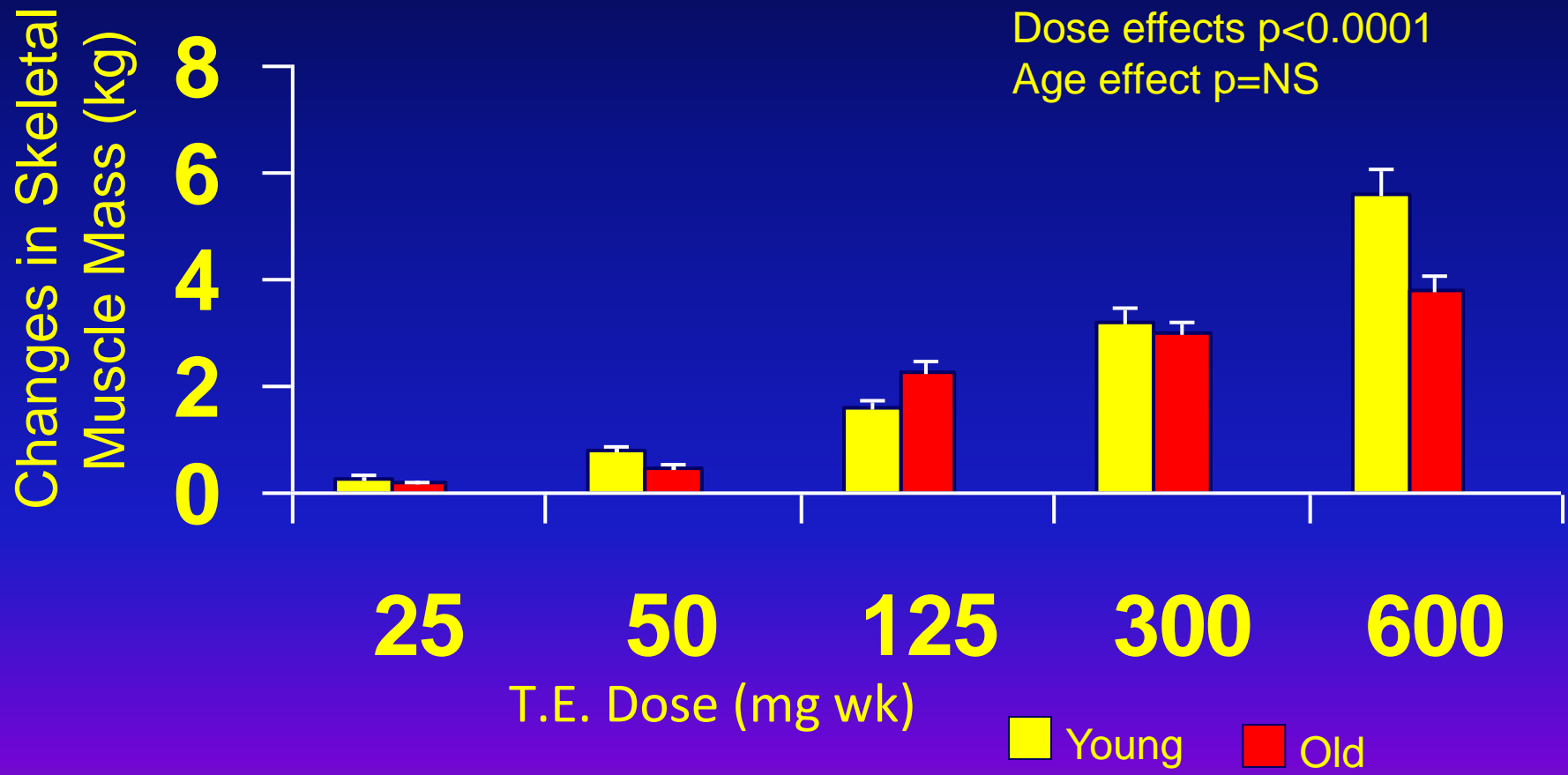
# Recommendation 5: Body Composition

- In hypogonadal men, testosterone administration improves body composition (decrease of fat mass, increase of lean body mass).

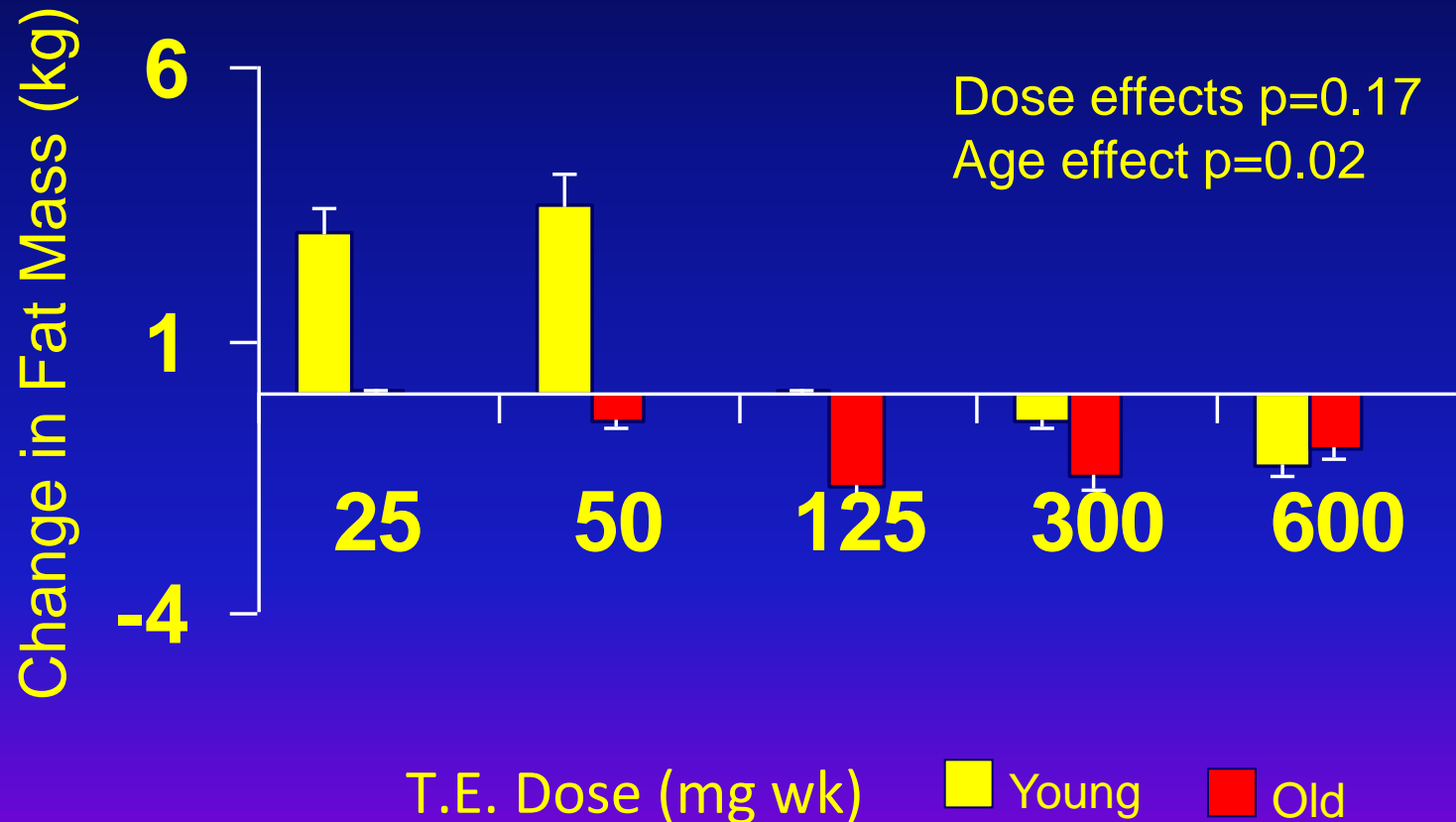
(Level 1b, Grade A).

- Secondary benefits of these changes of body composition on strength, muscle function, metabolic and cardiovascular dysfunction are suggested by available data but require confirmation by large-scale studies

# 20-wk, randomized, double-blind study of combined treatment with GnRH agonist plus one of five doses of testosterone



# 20-wk, randomized, double-blind study of combined treatment with GnRH agonist plus one of five doses of testosterone enanthate (TE)

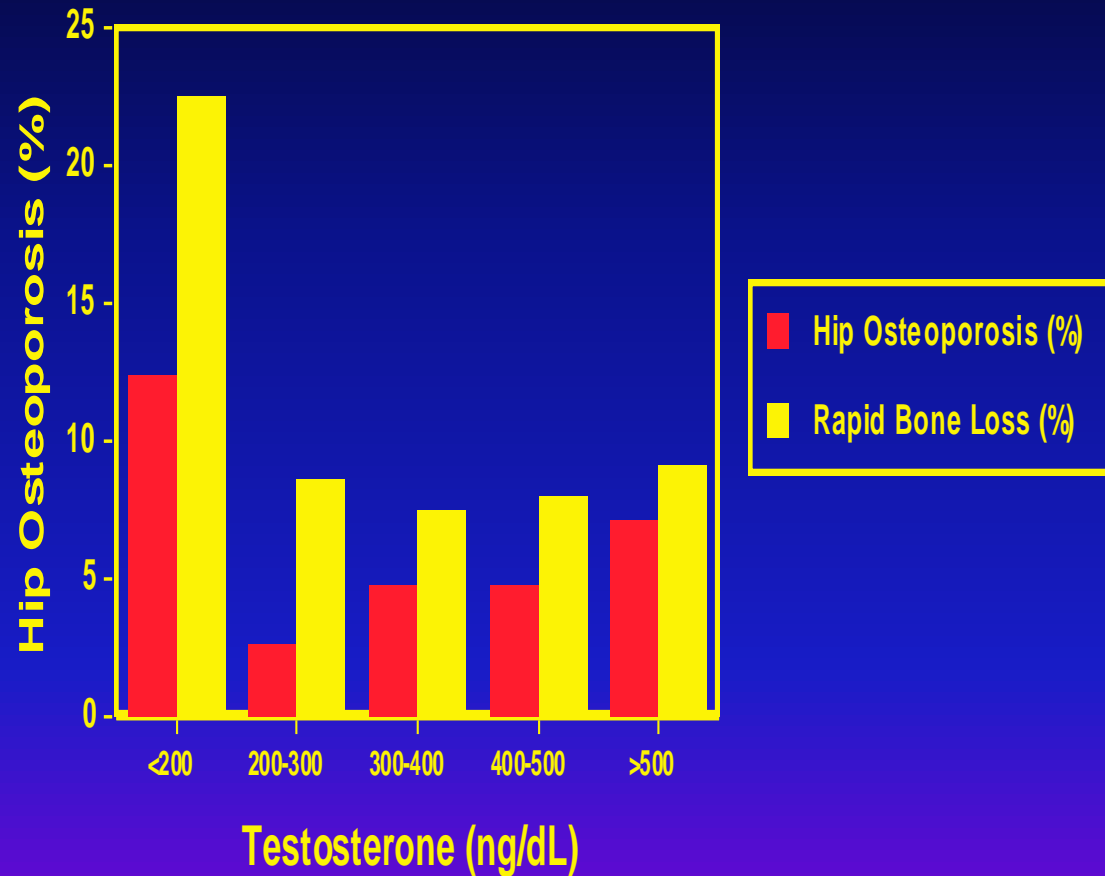


# Recommendation 6: Bone Density And Fracture Rate

- Osteopenia, osteoporosis and fracture prevalence rates are greater in hypogonadal younger and older men. [Bone density in hypogonadal men of all ages increases under testosterone substitution [ (Level 1b, Grade A).
- Fracture data are not yet available and thus the long term benefit of testosterone requires further investigation.
- Assessment of bone density at 2-year intervals is advisable in hypogonadal men and serum testosterone measurements should be obtained in all men with osteopenia

# What is hypogonadism (for the skeleton)?

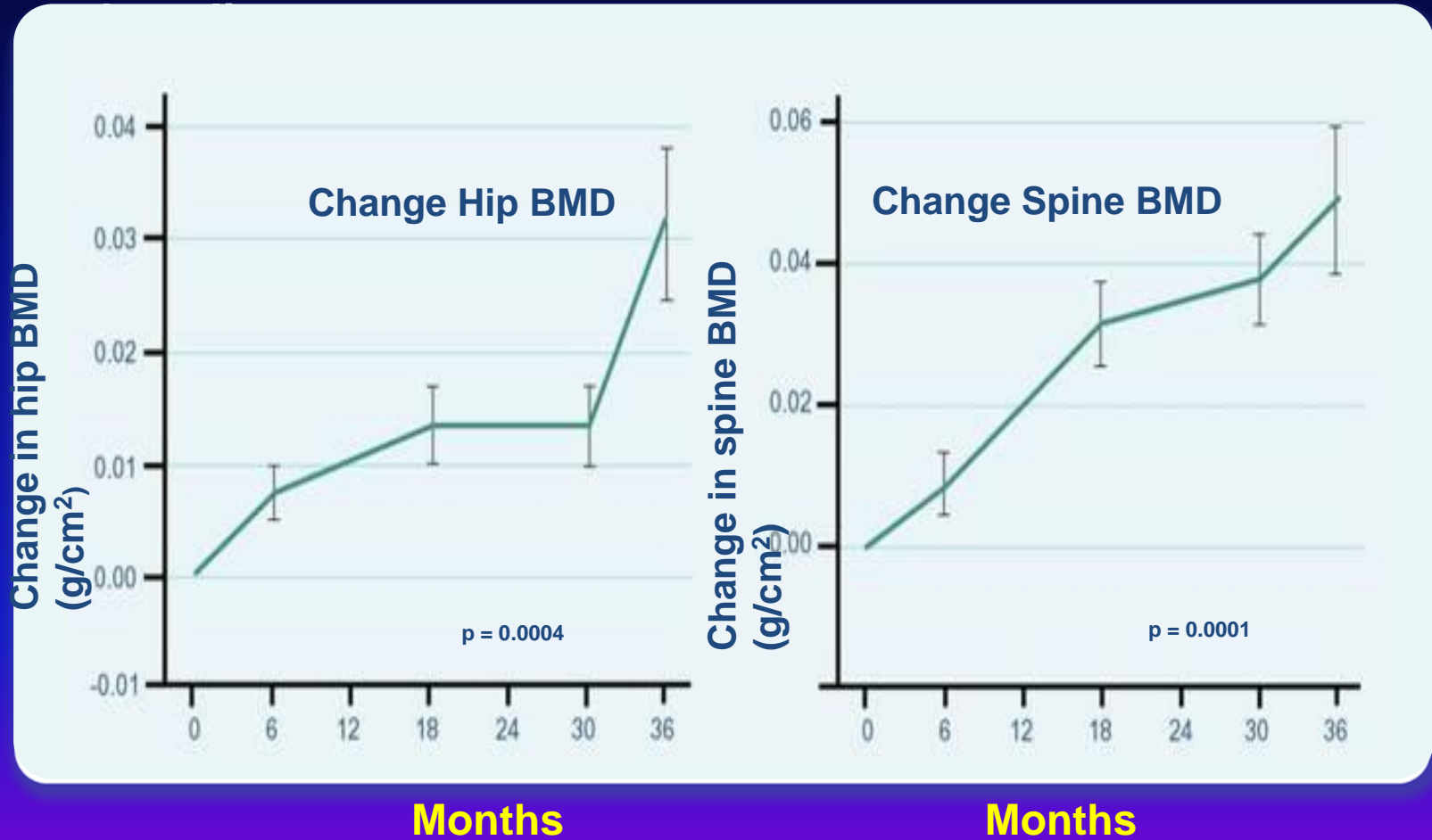
- 2447 men age 65 and over
- BMD of hip and spine by DXA
- Followed for a mean of 1.8 years
- Rapid bone loss defined as  $> 3\%$  per year



Fink et al JCEM 91:3908, 2006

# Testosterone Gel Effects on Bone Mineral Density (3 Years)

BMD showed significant gradual and progressive increase from



Wang C, Cunningham G *et al.* J Clin Endo Metab 2004;  
89:2085-98.

# Recommendation 7: 1

## Testosterone And Sexual Function

- The initial assessment of all men with erectile dysfunction and/or diminished libido should include determination of serum testosterone.
- These dysfunctions, with or without a testosterone deficiency might be related to co-morbidities (i.e. diabetes mellitus, hyperprolactinemia, the metabolic syndrome, bladder outlet obstruction, peripheral vascular disease or medications)
- **Level 2a, Grade A.**

# Recommendation 7: 2.

## Testosterone And Sexual Function

- 7.2. Men with erectile dysfunction and/or diminished libido and documented testosterone deficiency are candidates for testosterone therapy.

**Level 2a, Grade A**

- An inadequate response to testosterone treatment requires reassessment of the causal mechanisms responsible for the erectile dysfunction

# Recommendation 7:3.

## Testosterone And Sexual Function

- 7.3. In the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels, a short (e.g. 3 months) therapeutic trial may be justified.
- An absence of response calls for discontinuation of testosterone administration.
- A satisfactory response might be placebo-generated, so that continued assessment is advisable before long-term treatment is recommended

**Level 2a, Grade B.**

# Recommendation 7: 4

## Testosterone And Sexual Function

- There is evidence suggesting therapeutic synergism with combined use of testosterone and phosphodiesterase-5 inhibitors in hypogonadal or borderline eugonadal men (Level 1b, Grade B).
- These observations are still preliminary and require additional study. However, the combination treatment should be considered in hypogonadal patients with ED failing to respond to either treatment alone.
- It is unclear whether men with hypogonadism and ED should be treated initially with PDE-5-I, testosterone or the combination of the two.

# Number of Valid Nocturnal Erections in 24 Hypogonadal Men with and without Testosterone and Sildenafil Treatment



Rochira V et al. J Androl 27(2): 165-175 (2006)

# Recommendation 8:1

## testosterone and obesity, metabolic syndrome and Type 2 diabetes

- Many of the components of the metabolic syndrome (obesity, hypertension, dyslipidemia, impaired glucose regulation and insulin resistance) are also present in hypogonadal men.
- Numerous epidemiological studies have established a close relationship between obesity and low serum testosterone levels in healthy men
- 20–64% of obese men have a low serum total or free testosterone levels.
- The metabolic syndrome and Type 2 diabetes mellitus are associated with low plasma testosterone. Serum testosterone should be measured in men with Type 2 diabetes mellitus with symptoms suggestive of testosterone deficiency (Level 2b, Grade A).

## Recommendation 8:2

### testosterone and obesity, metabolic syndrome and Type 2 diabetes

- The effects of testosterone administration on glycemic control of men with diabetes mellitus are much less certain
- It is premature to recommend testosterone treatment for the metabolic syndrome or diabetes mellitus in the absence of laboratory and other clinical evidence of hypogonadism.
- In men with hypogonadism and diabetes and or the metabolic syndrome, testosterone treatment for traditional hypogonadal symptoms may have other unproven benefits on their metabolic status (Level 2a, Grade B).

# Recommendation 9:1

## prostate cancer and BPH

- At the present time, there is no conclusive evidence that testosterone therapy increases the risk of prostate cancer or BPH.
- There is also no evidence that testosterone treatment will convert sub-clinical prostate cancer to clinically detectable prostate cancer (Level 4, Grade C)
- However, there is unequivocal evidence that testosterone can stimulate growth and aggravate symptoms in men with locally advanced and metastatic prostate cancer
- (Level 2a, Grade A).

# Charles Huggins



# **Dr Charles Huggins**

## **Nobel Laureate**

**Dr. Huggins, in collaboration with his students Clarence V. Hodges and William Wallace Scott, published three papers in 1941 that demonstrated the relationship between the endocrine system and the normal functioning of the prostate gland. They also showed that removal of the testicles or administration of estrogens which would neutralize the male hormones--they could cause regression of prostate tumors.**

# Recommendation 9:1

## prostate cancer and BPH

- Currently, adequately powered and optimally designed long-term prostate disease data are not available to determine whether there is any additional risk from testosterone replacement.
- Hypogonadal older (>45 years) men should be counseled on the potential risks and benefits of testosterone replacement before treatment and carefully monitored for prostate safety during treatment **(Level 3, Grade A)**.

# Recommendation 9:2

## prostate cancer and BPH

- Prior to therapy with testosterone, a man's risk of prostate cancer must be assessed using, as a minimum, digital rectal examination (DRE) and determination of serum prostate-specific antigen (PSA). However, the pre-treatment assessment can be improved by incorporating other risk predictors such as age, family history, and ethnicity/race. If the patient and physician feel that the risk is sufficiently high, further assessment may be desirable (Level 2a, Grade B).
- However, pre-treatment prostate ultra-sound examinations or biopsies are not recommended as routine requirements.

Wang et al *Aging Male*. 1-8.2008.

# Recommendation 9:3

## prostate cancer and BPH

- After initiation of testosterone treatment, patients should be monitored for prostate disease at 3–6 months, 12 months, and at least annually thereafter (Level 3, Grade C).
- Should the patient's prostate cancer risk be sufficiently high (suspicious finding on DRE; increased PSA or as calculated using a combination of risk factors) trans-rectal ultrasound-guided biopsies of the prostate are indicated (Level 2b, Grade A).

# Recommendation 9:4

## prostate cancer and BPH

- Severe symptoms of lower urinary tract symptoms (LUTS) evident by a high (>21) International Prostate Symptom Score (IPSS) due to benign prostate hyperplasia represents a relative contraindication (although there are no compelling data to suggest that testosterone treatment causes exacerbation of LUTS or promote acute urinary retention) (Level 3, Grade C).
- After successful treatment of lower urinary tract obstruction, this contraindication is no longer applicable (Level 4, Grade C).

# Recommendation 9:4

## prostate cancer and BPH

- Men successfully treated for prostate cancer and suffering from symptomatic hypogonadism are potential candidates for testosterone substitution after a prudent interval if there is no clinical or laboratory evidence of residual cancer.
- As long-term outcome data are not available, clinicians must exercise good clinical judgment together with adequate knowledge of advantages and drawbacks of testosterone therapy in this situation (**Level 2b, Grade C**).
- The risk and benefits must be clearly discussed with and understood by the patient and the follow-up must be particularly careful.

Wang et al *Aging Male*. 1-8.2008.

# Recommendation 10:

## Treatment And Delivery systems

- Preparations of natural testosterone should be used for substitution therapy.
- Currently available intramuscular, subdermal, transdermal, oral and buccal preparations of testosterone are safe and effective (Level 1b, Grade A).
- The treating physician should have sufficient knowledge and adequate understanding of the pharmacokinetics as well as of the advantages and drawbacks of each preparation.
- The selection of the preparation should be a joint decision of an informed patient and physician

# Recommendation 10:2

## Treatment And Delivery systems

- Because the possible development of an adverse event during treatment (especially elevated hematocrit or prostate carcinoma) requires rapid discontinuation of testosterone substitution, short-acting preparations may be preferred over long acting depot preparations in the initial treatment of patients with LOH (Level 4, Grade C)

# Recommendation 10:3

## Treatment And Delivery Systems

- Inadequate data are available to determine the optimal serum testosterone level for efficacy and safety.
- For the present time, mid-to-lower young adult male serum testosterone levels seem appropriate as the therapeutic goal
- Sustained supra-physiological levels should be avoided.
- No evidence exists for or against the need to maintain the physiological circadian rhythm of serum testosterone levels (Level 3, Grade B).

# Recommendation 10:4-6

## Treatment And Delivery Systems

- 17-a-alkylated androgen preparations such as 17a-methyl testosterone are obsolete because of their potential liver toxicity and should no longer be prescribed (Level 2b, Grade A).
- There is not enough evidence to recommend substitution of DHT in aging men;
- Other non-testosterone androgen precursor preparations such as DHEA, DHEA-S, androstenediol or androstenedione are not recommended (Level 1b ,Grade A).

# Recommendation 11:2

- Men with significant erythrocytosis (hematocrit >52%) (Level 3, Grade A),
- untreated obstructive sleep apnoea (Level 3, Grade B),
- untreated severe congestive heart failure (Level 3, Grade B)

should not be started on treatment with testosterone without prior resolution of the comorbid condition

Wang et al *Aging Male*. 1-8.2008].

# Recommendation 11:3

## Adverse Effects And Monitoring

- Erythrocytosis can develop during testosterone treatment, especially in older men treated by injectable testosterone preparations.
- Periodic hematological assessment is indicated, i.e. before treatment, then 3–4 and 12 months in the first year of treatment and annually thereafter.
- Although it is not yet clear what critical threshold is desirable, dose adjustments may be necessary to keep hematocrit below 52–55%  
(Level 3, Grade A).

# Conclusion

- The diagnosis of late onset testosterone deficiency is based on the presence of symptoms or signs and persistent low serum testosterone levels.
- The benefits and risks of testosterone therapy must be clearly discussed with the patient and assessment of prostate and other risk factors considered before commencing testosterone treatment.

- .

# Conclusion

- Response to testosterone treatment should be assessed.
- If there is no improvement of symptoms and signs, treatment should be withdrawn and the patient investigated for other possible causes of the clinical presentations.

The writing group with expert representatives from the International Society of Andrology (ISA), The international Society of the study of the aging Male (ISSAM), European association of Urology (EAU), European Academy of Andrology (EAA) and American Society of Andrology (ASA) and additional urologists.

- CHRISTINA WANG,  
EBERHARD NIESCHLAG,  
RONALD S. SWERDLOFF,  
HERMANN BEHRE  
WAYNE J. HELLSTROM,  
LOUIS J. GOOREN,  
JEAN M. KAUFMAN,  
JEAN-JACQUES LEGROS,
- BRUNO LUNENFELD,  
ALVARO MORALES,  
JOHN E. MORLEY,  
CLAUDE SCHULMAN,  
IAN M. THOMPSON,  
WOLFGANG WEIDNER,  
FREDERICK C. W. WU



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BUDAPEST, HUNGARY

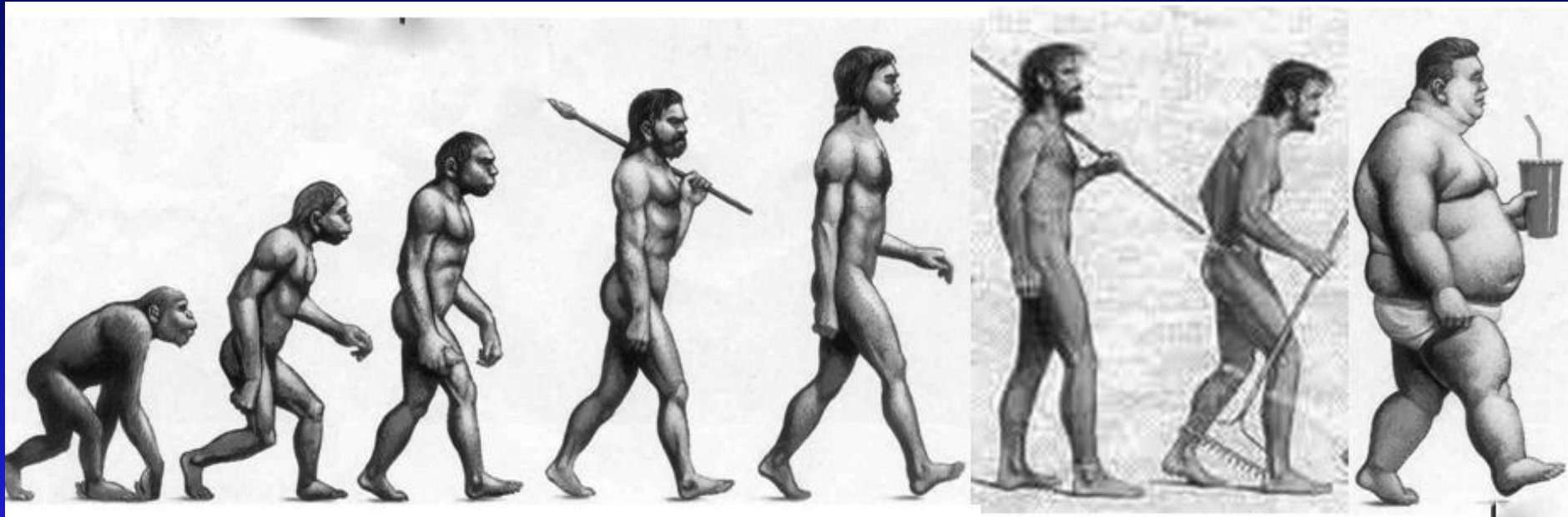


See You In Budapest

2<sup>nd</sup> EUROPEAN CONGRESS  
ON THE AGING MALE



# The Development Of The Homo Sapiens



Thank you for your attention