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# Increasing complexity and challenges in Male hypogonadism

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# Conflict of Interest

- During the last three years, we have received educational and research grants from scientific societies and pharmaceutical companies.
- None of these can be considered as conflict of interest for this lecture.

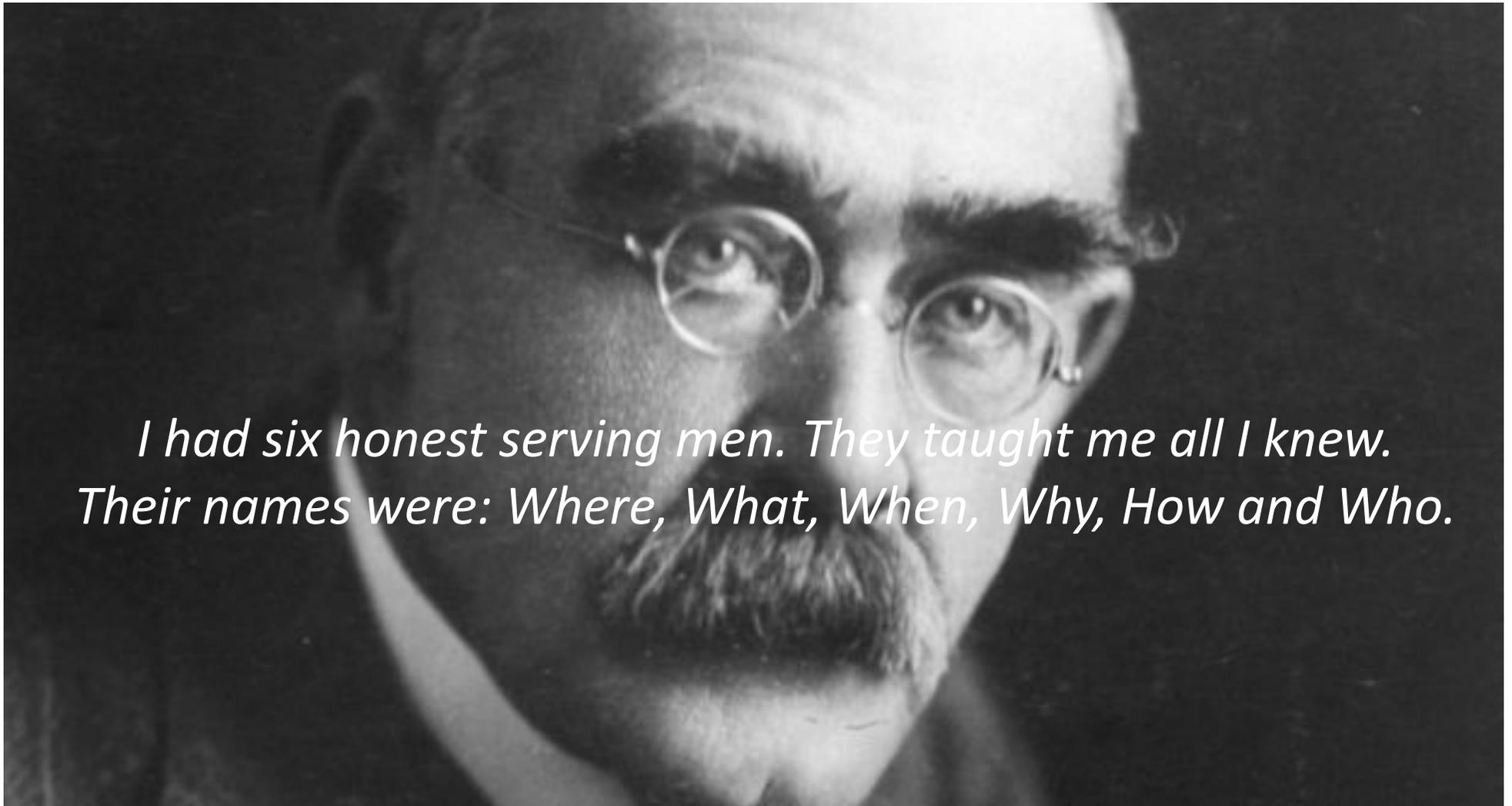
# What we will do

- Provide current concepts of male hypogonadism
- Discuss practical issues of testosterone supplementation
- Emerge the role of life-style interventions on the management of male hypogonadism

## What we will not do

- Go in details for each individual study
- Stack in controversies and “grey areas”





*I had six honest serving men. They taught me all I knew.  
Their names were: Where, What, When, Why, How and Who.*

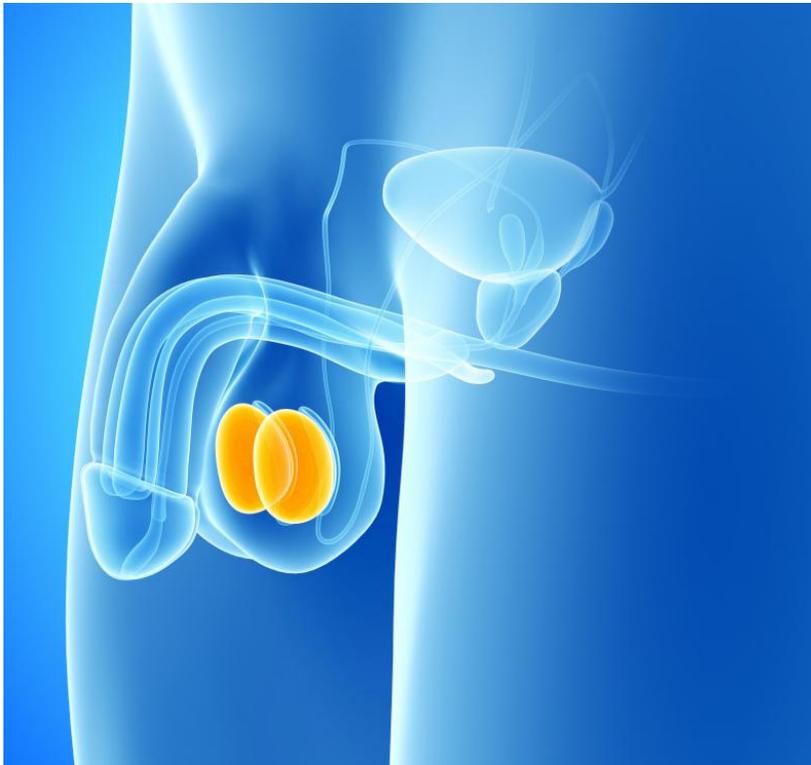
Rudyard Kipling (1865 - 1936)



# What?

What is male hypogonadism?

# Testicular function



- Failure of endocrine function
  - Low serum testosterone
  - Male hypogonadism
- Failure of exocrine function
  - Poor sperm quality
  - Male infertility

# Testicular function

Hypogonadism → Infertility



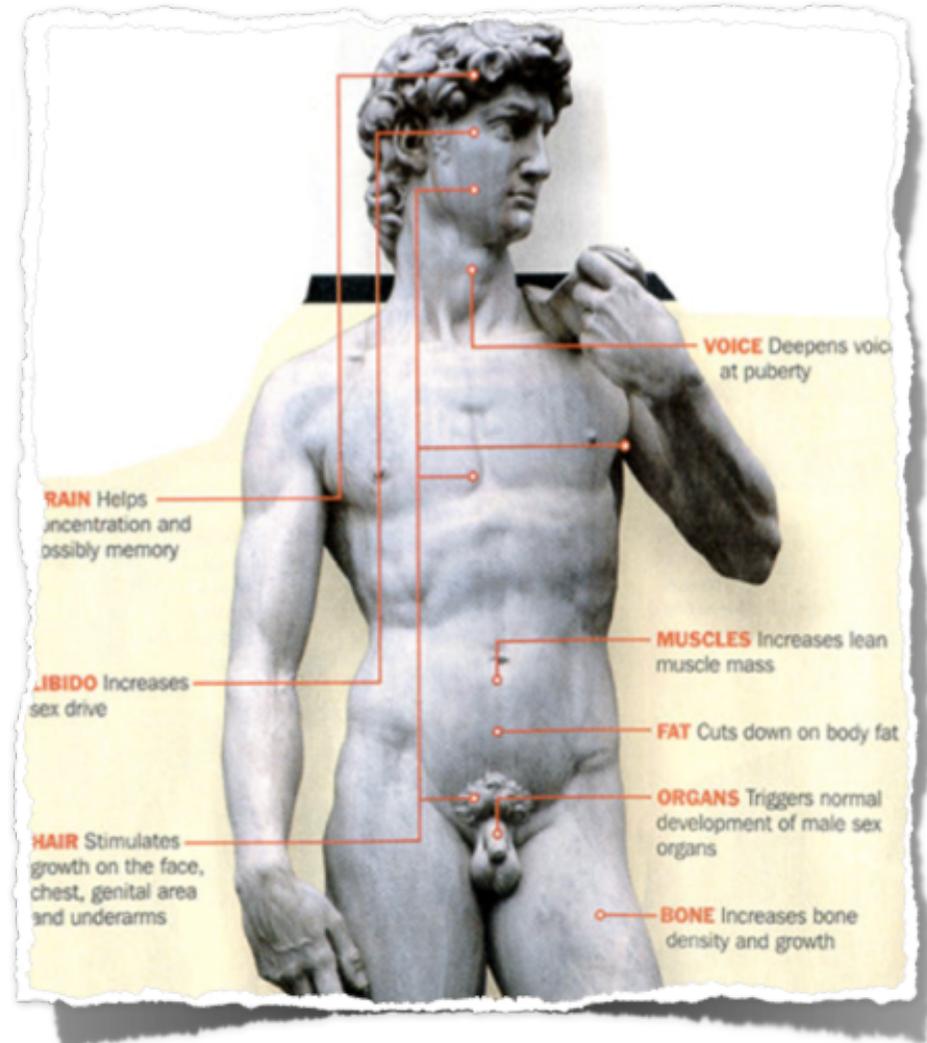
Infertility → Hypogonadism



# What?

What is the clinical picture of male hypogonadism?

# Testosterone actions





# Clinical picture

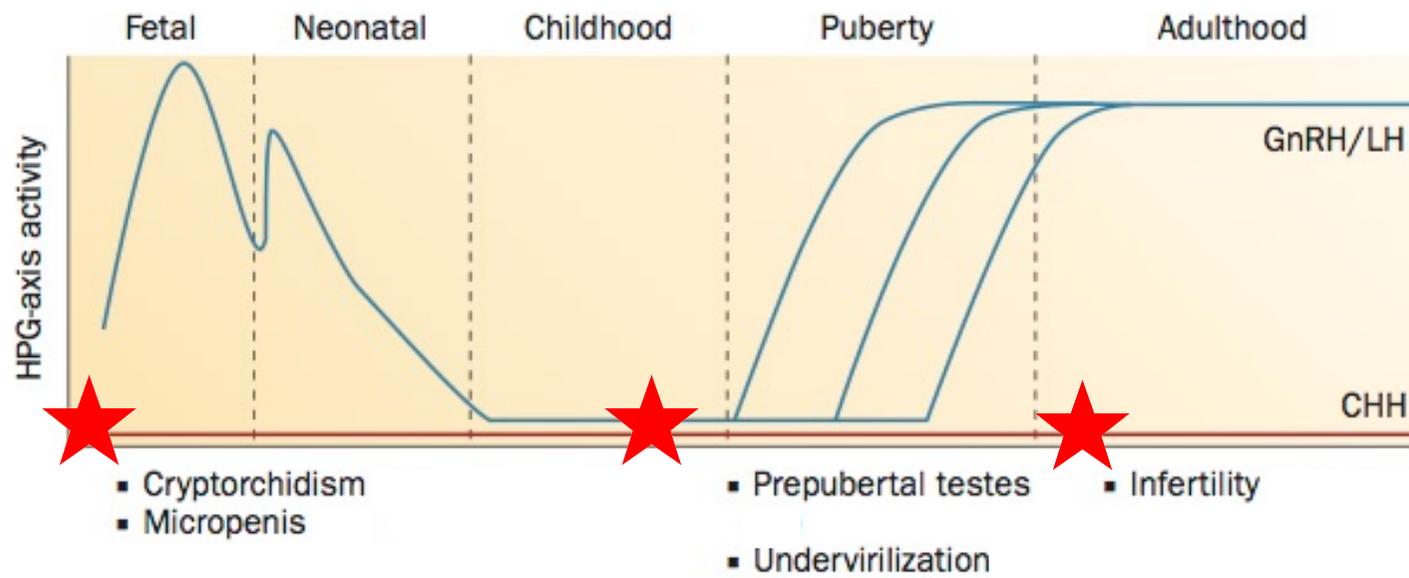
## **High specificity**

- Low libido
- Decreased morning erections
- Loss of body hair
- Low bone mineral density (BMD)
- Gynecomastia
- Small testes

## **Low specificity**

- Fatigue
- Depression
- Anemia
- Reduced muscle strength
- Increased fat mass

# Hypogonadism according to age



# Massachusetts Male Aging Study

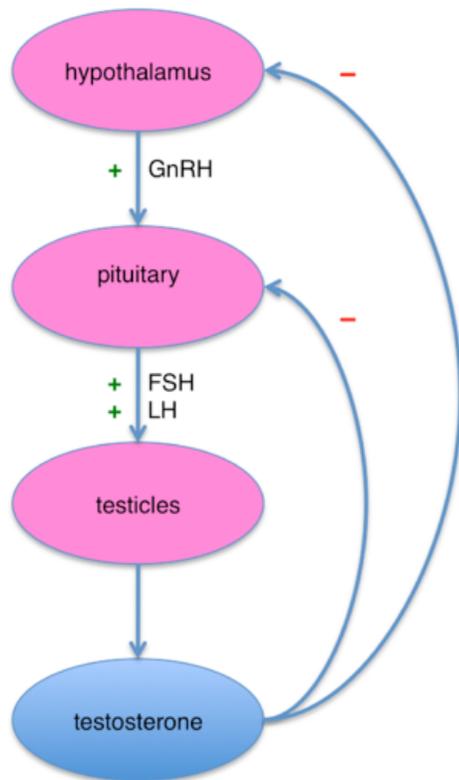
- Relative Risk (adjusted for age) for males with total T < 200 ng/dl in comparison to males with total T 400 - 600 ng/dl:
  - 1.93 for overall mortality
  - 3.30 for disease-specific mortality (cancer)
  - 1.93 for disease-specific mortality (cardiovascular disease)



# What?

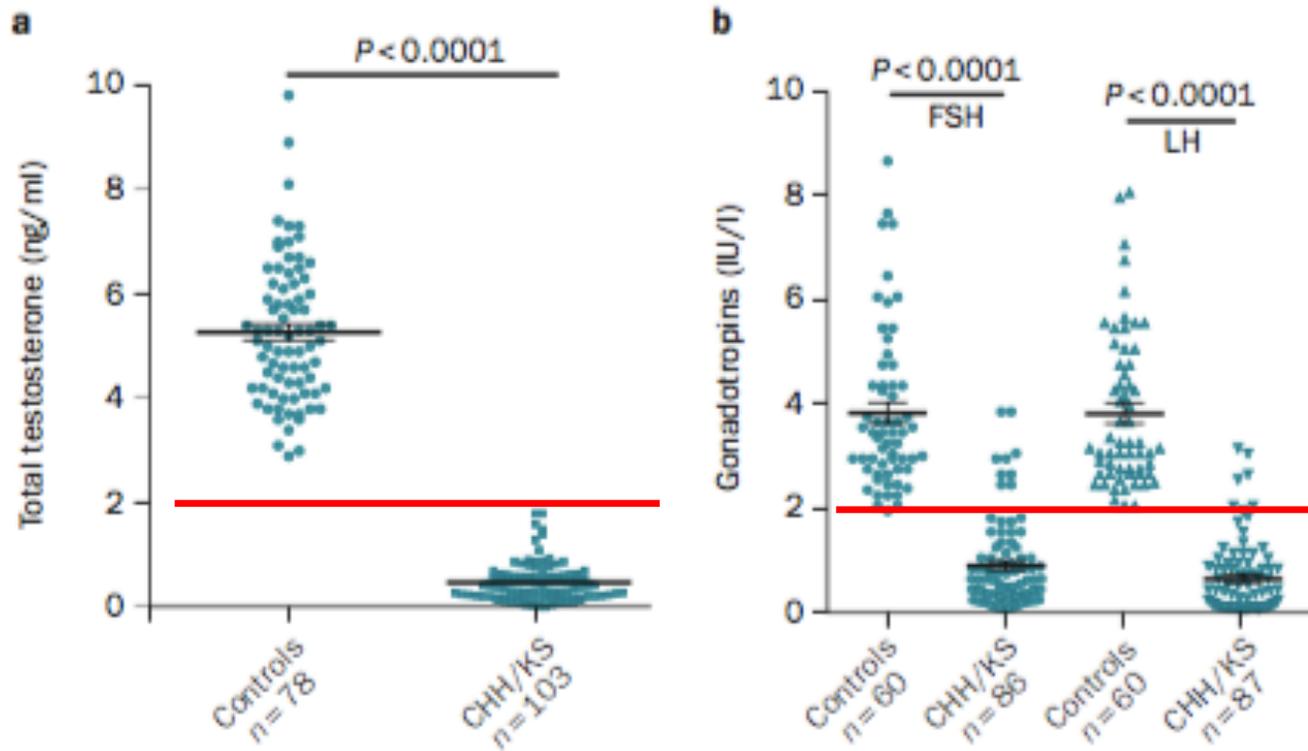
What are the types of hypogonadism?

# Hypogonadotropic hypogonadism



- Failure at the hypothalamus – pituitary level
- Kallmann's syndrome

# Hormonal profile



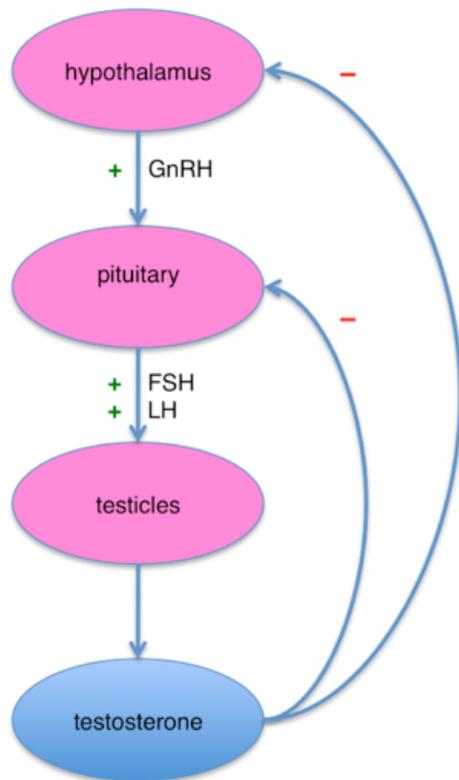
Trabado S et al. J Clin Endocrinol Metab 2014;99:E268  
Young J. J Clin Endocrinol Metab 2012;97:707

## Causes of hypogonadotropic (secondary) hypogonadism

Acquired
Tumors
Benign tumors and cysts
Craniopharyngiomas
Germinomas, meningiomas, gliomas, astrocytomas
Metastatic tumors (breast, lung, prostate)
"Functional" gonadotropin deficiency
Chronic systemic disease
Acute illness
Malnutrition
Hypothyroidism, hyperprolactinemia, diabetes mellitus, Cushing's disease
Anorexia nervosa, bulimia
Post-androgen abuse
Infiltrative diseases
Hemochromatosis
Granulomatous diseases
Histiocytosis
Head trauma
Pituitary apoplexy
Drugs - Marijuana
Congenital
Isolated GnRH deficiency
Without anosmia
Kallmann syndrome
Associated with adrenal hypoplasia congenita
GnRH deficiency associated with mental retardation/obesity
Laurence-Moon-Biedl syndrome
Prader-Willi syndrome
Idiopathic forms of multiple anterior pituitary hormone deficiencies
Congenital malformations often associated with craniofacial anomalies

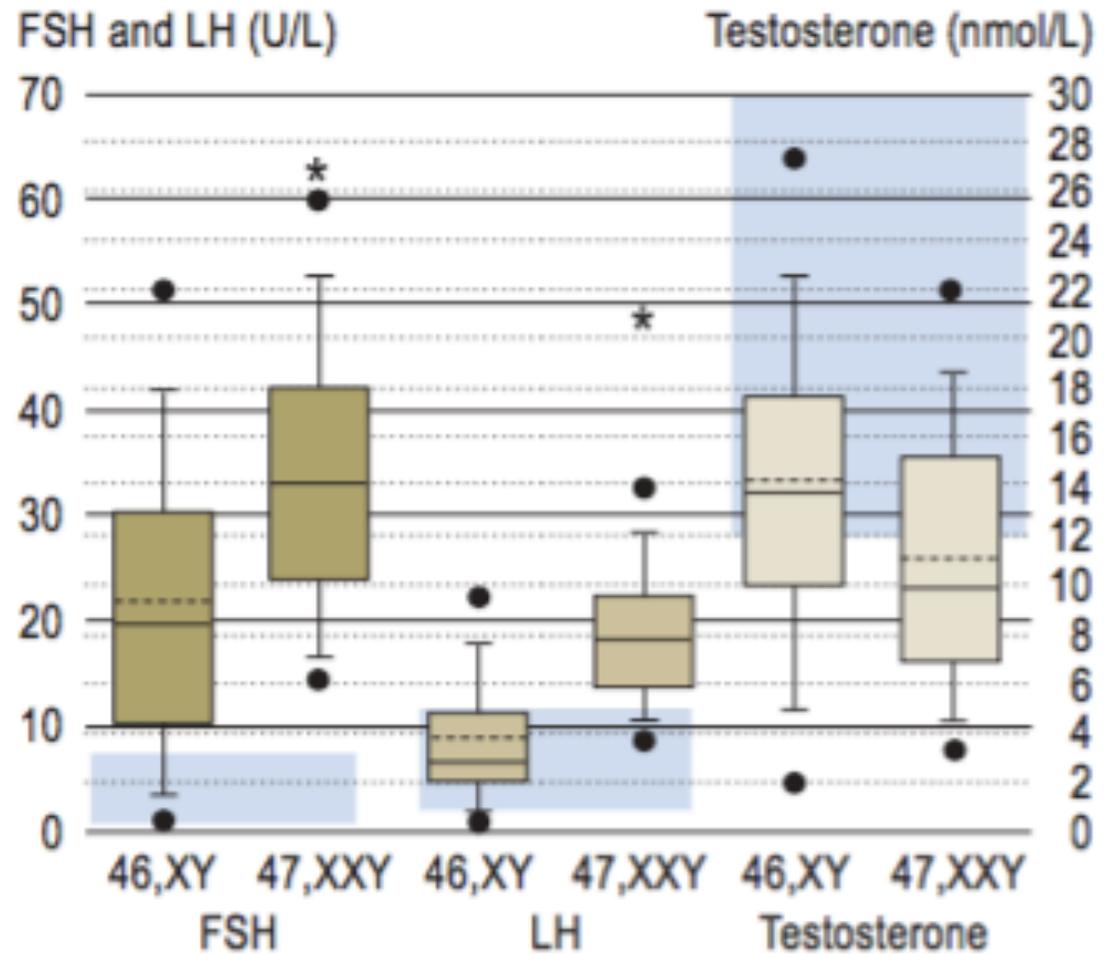
GnRH: gonadotropin-releasing hormone.

# Hypergonadotropic hypogonadism



- Failure at the testicular level
- Klinefelter's syndrome

# Hormonal profile

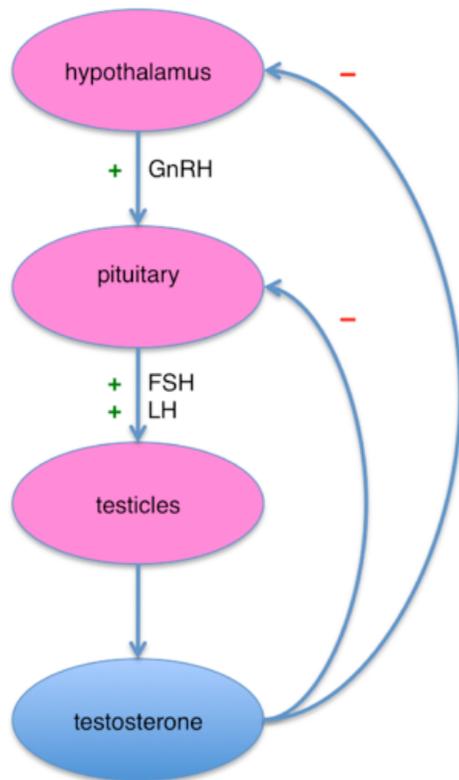


## Causes of primary hypogonadism in males

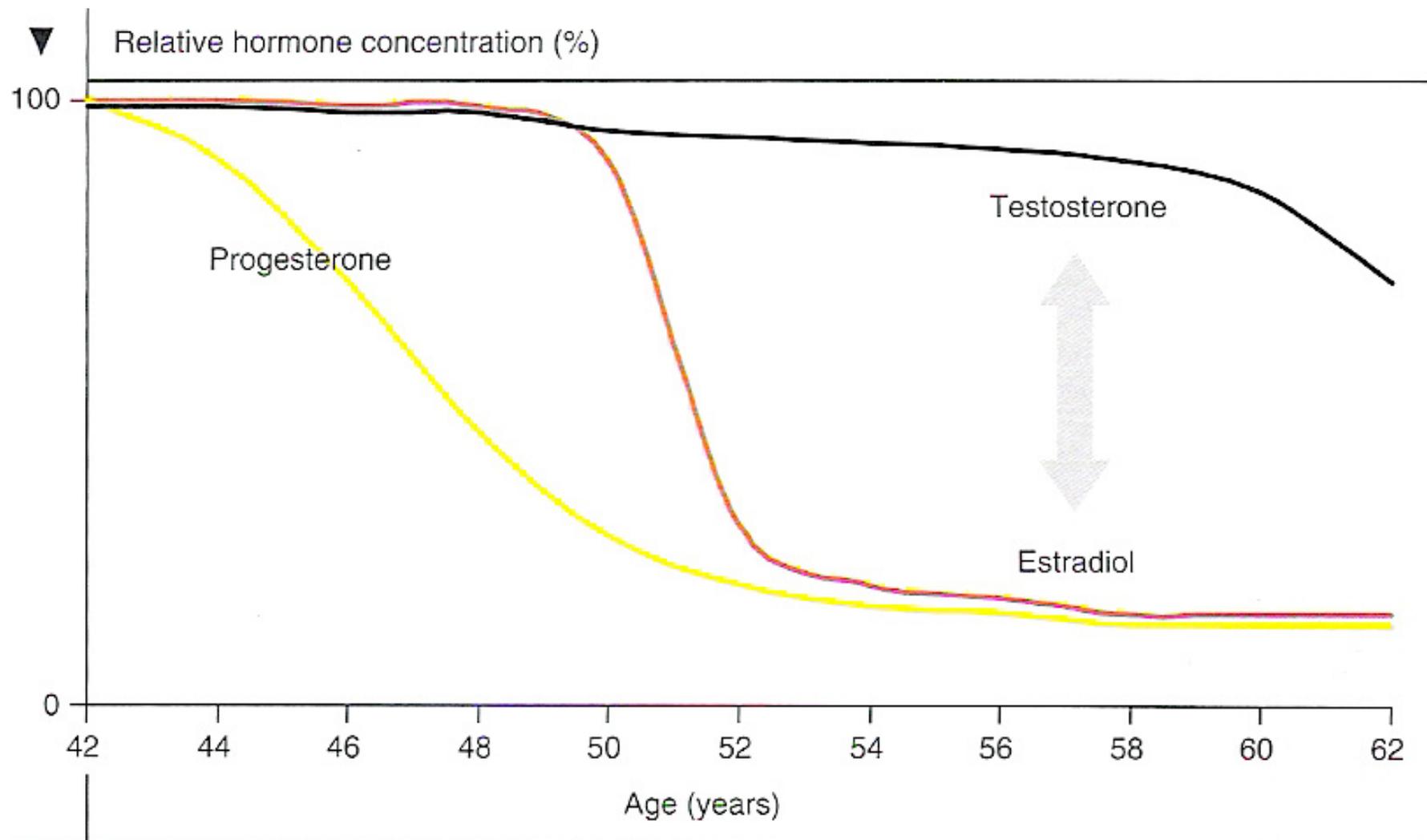
<b>Congenital abnormalities</b>
Klinefelter syndrome
Other chromosomal abnormalities
Mutation in the FSH and LH receptor genes
Cryptorchidism
Varicocele
Disorders of androgen synthesis
Myotonic dystrophy
<b>Acquired diseases</b>
Infections, especially mumps
Radiation
Alkylating agents
Suramin
Ketoconazole
Glucocorticoids
Environmental toxins
Trauma
Testicular torsion
Autoimmune damage
Chronic systemic illnesses
Hepatic cirrhosis
Chronic renal failure
AIDS
Idiopathic

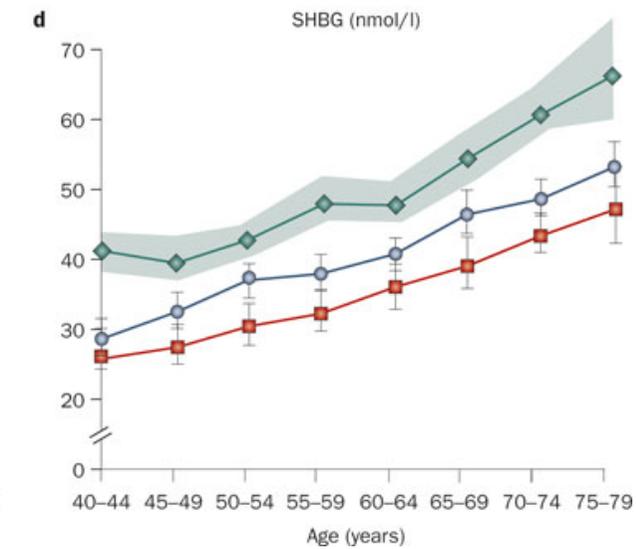
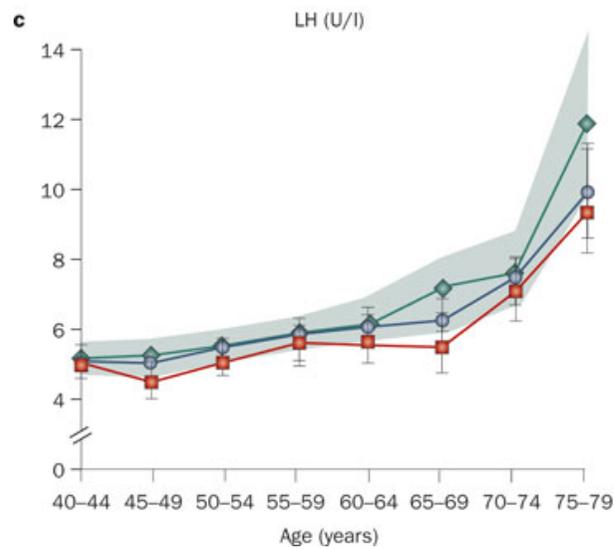
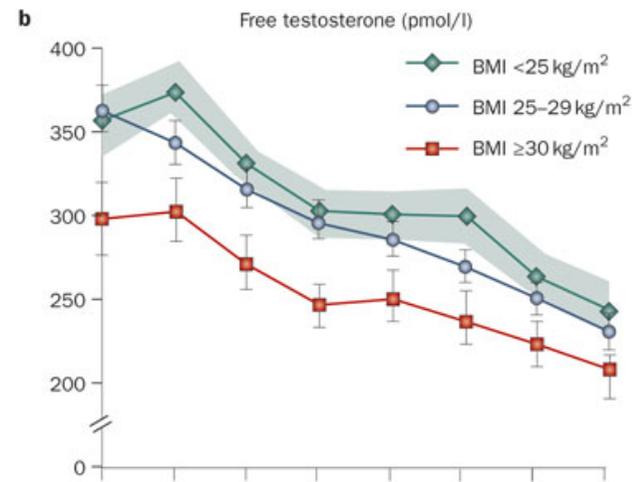
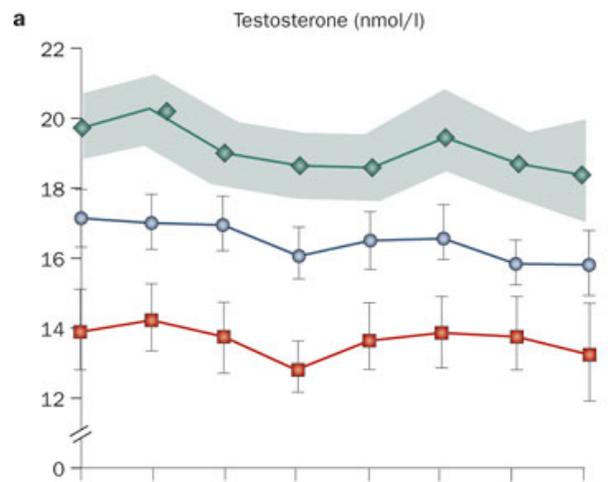
FSH: follicle-stimulating hormone; LH: luteinizing hormone; AIDS: acquired immunodeficiency syndrome.

# Late-onset hypogonadism

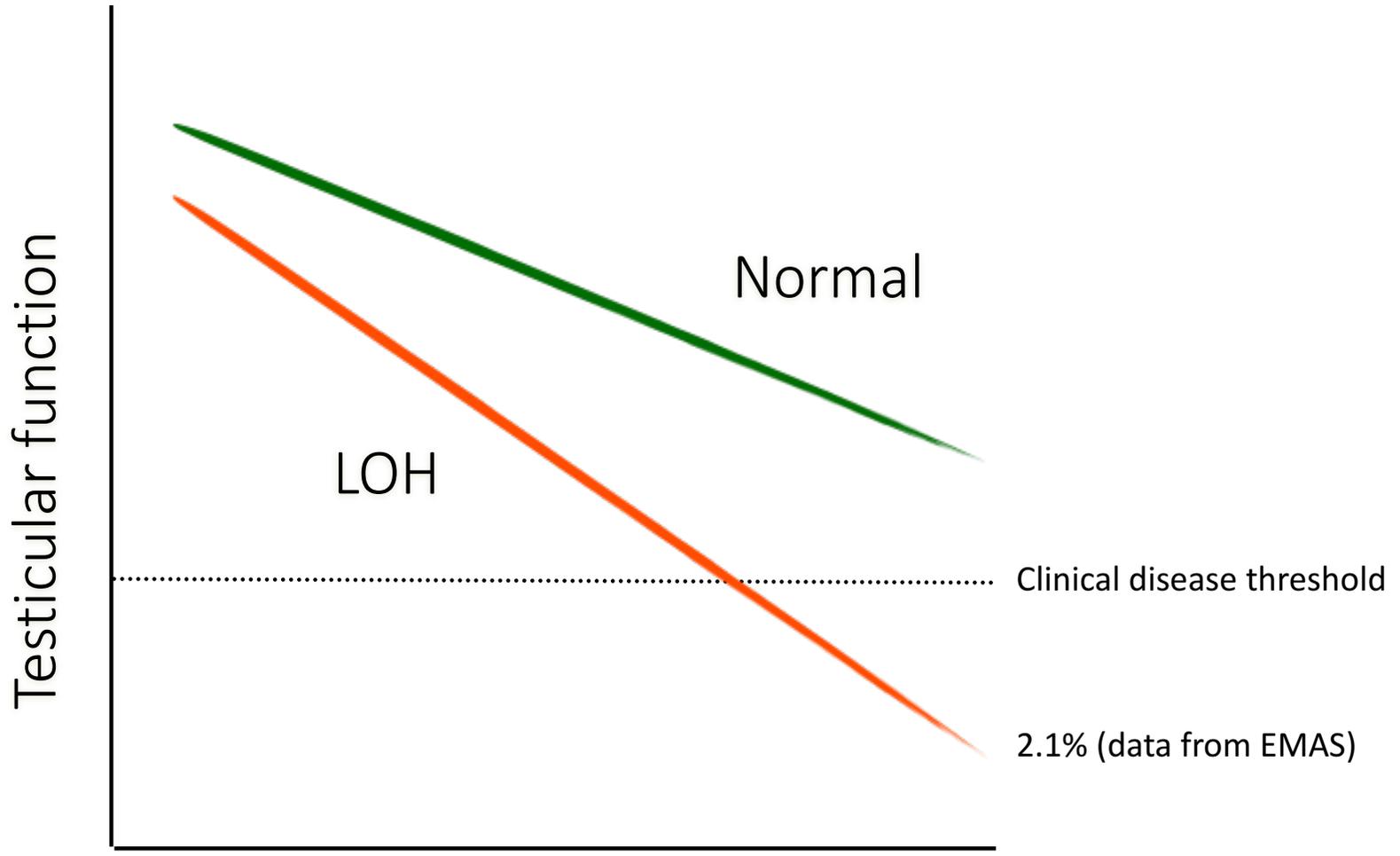


- Failure at both hypothalamus – pituitary and testicular level
- Associated with advanced age
- Clinical picture
- Hormonal profile





LOH



Time

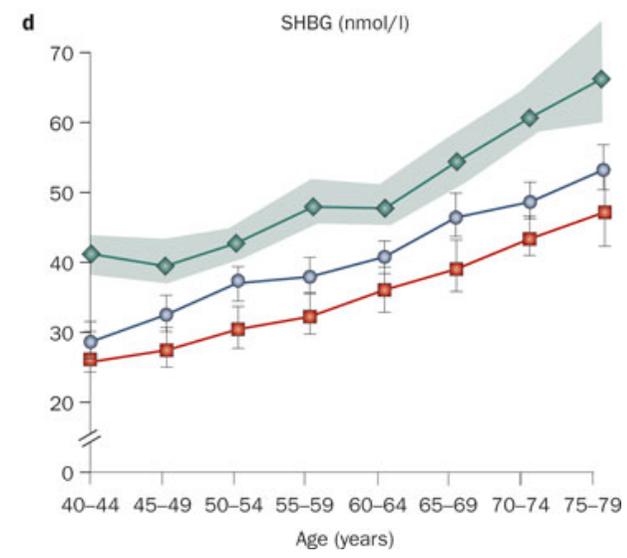
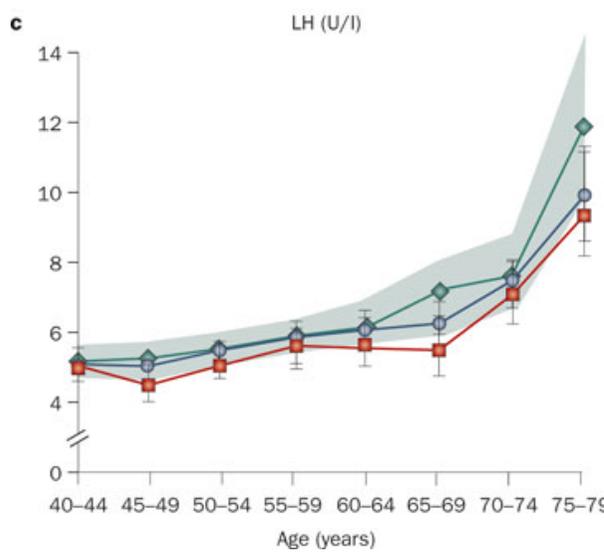
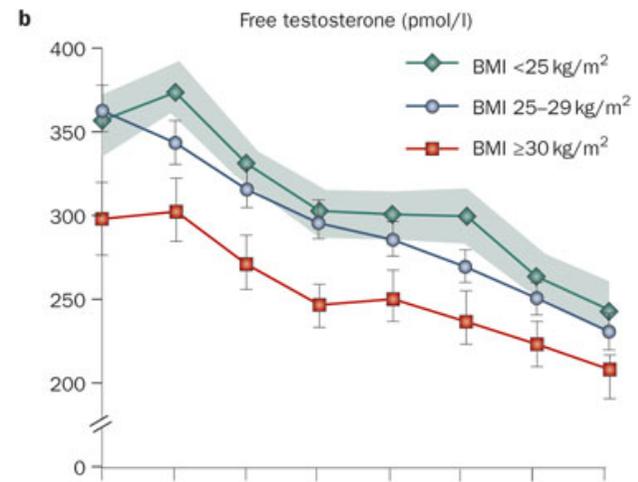
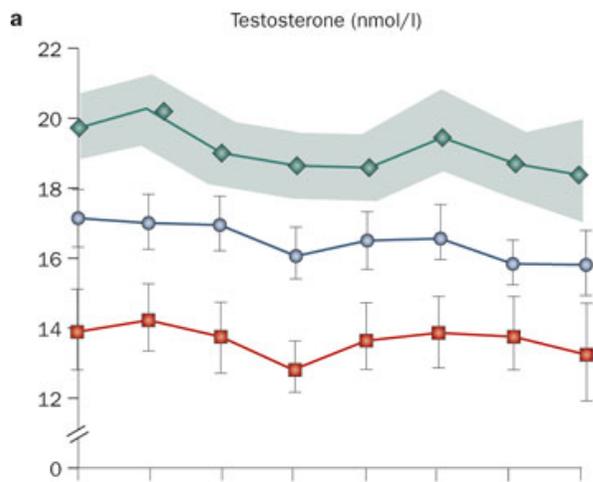
# What?

When else do we have to take under consideration?

# Metabolic syndrome: definitions

<b>Table 1. Definitions of the metabolic syndrome.</b>					
Organization	<b>WHO</b>	<b>EGIR</b>	<b>AACE</b>	<b>NCEP / ATP III</b>	<b>IDF</b>
Year	<b>1999</b>	<b>1999</b>	<b>2003</b>	<b>2005</b>	<b>2005</b>
Reference no.	(15)	(16)	(17)	(18,19)	(20)
<b>Required</b>	insulin resistance (top 25 percent) OR glucose > 110 mg/dL OR 2-h glucose > 140 mg/dL	insulin resistance OR fasting hyperinsulinemia (top 25 percent)	high risk of insulin resistance OR BMI 25 kg/m <sup>2</sup> OR waist > 102 cm (M) OR waist > 88 cm (F)		waist > 94 cm (M) OR > 80 cm (F)*
<b>Additional</b>	PLUS two of the following:	PLUS two of the following:	PLUS two of the following:	three of the following:	PLUS two of the following:
Glucose		110-125 mg/dL	> 110 mg/dL OR 2-hour glucose > 140 mg/dL	> 100 mg/dL OR "on treatment"	> 100 mg/dL OR diabetes
Blood pressure	> 140 / 90 mm Hg	> 140 / 90 mm Hg OR "on treatment"	> 130 / 85 mm Hg	> 130 / 85 mm Hg OR "on treatment"	> 130 / 85 mm Hg OR "on treatment"
HDL-cholesterol	< 35 mg/dL (M) OR < 40 mg/dL (F)	< 40 mg/dL	< 40 mg/dL (M) OR < 50 mg/dL (F)	< 40 mg/dL (M) OR < 50 mg/dL (F) OR "on treatment"	< 40 mg/dL (M); OR < 50 mg/dL (F) OR "on treatment"
Triglycerides	OR > 150 mg/dL	OR > 180 mg/dL OR "on treatment"	> 150 mg/dL	> 150 mg/dL OR "on treatment"	> 150 mg/dL OR "on treatment"
Obesity	waist/hip ratio > 0.9 (M) OR > 0.85 (F) OR BMI > 30 kg/m <sup>2</sup>	waist > 94 cm (M) OR > 80 cm (F)		waist > 102 cm (M) OR > 88 cm (F)	

EGIR: European Group for the Study of Insulin Resistance, WHO: World Health Organization, AACE: American Association of Clinical Endocrinologists, NCEP / ATP III: National Cholesterol Education Program / Adult Treatment Panel III, IDF: International Diabetes Federation, (M): males, (F): females, BMI: body mass index, HDL: high density lipoprotein.



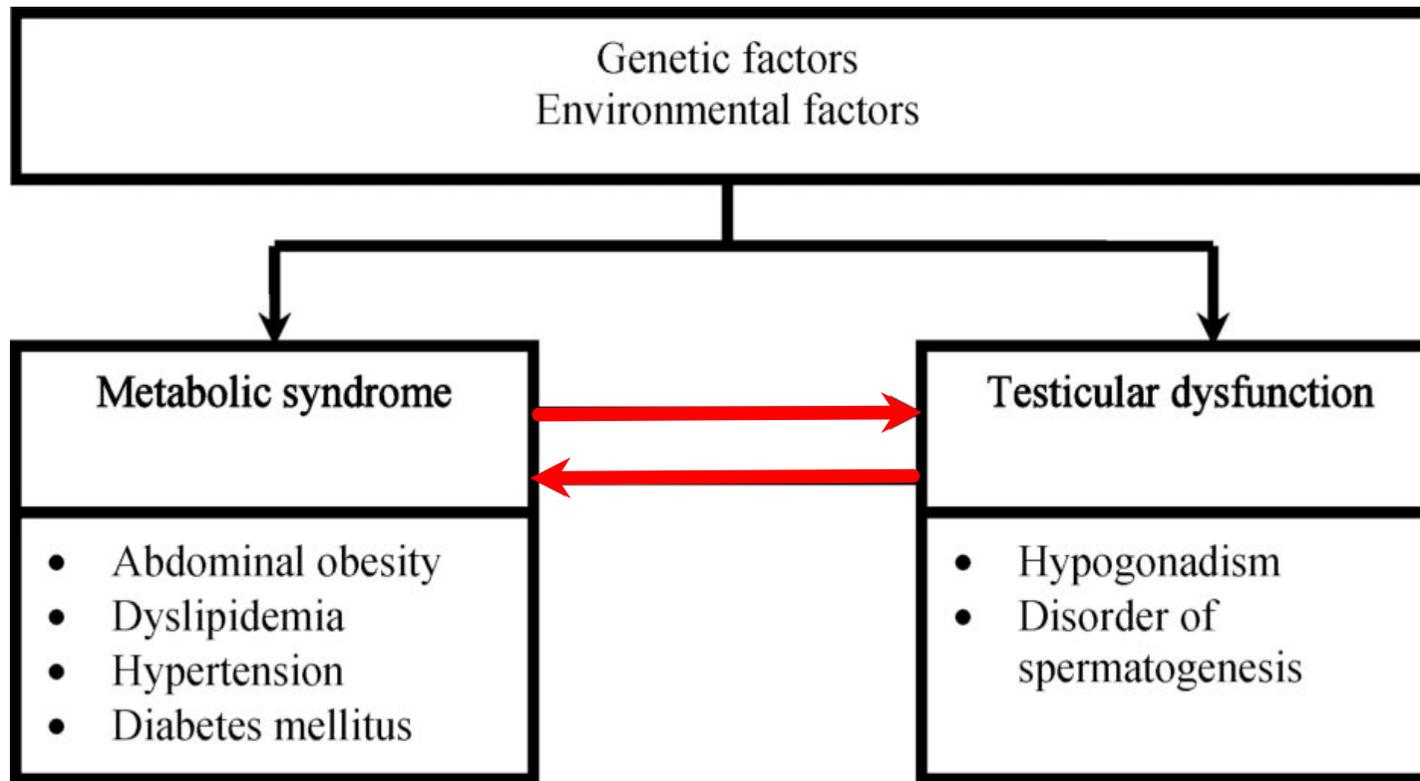
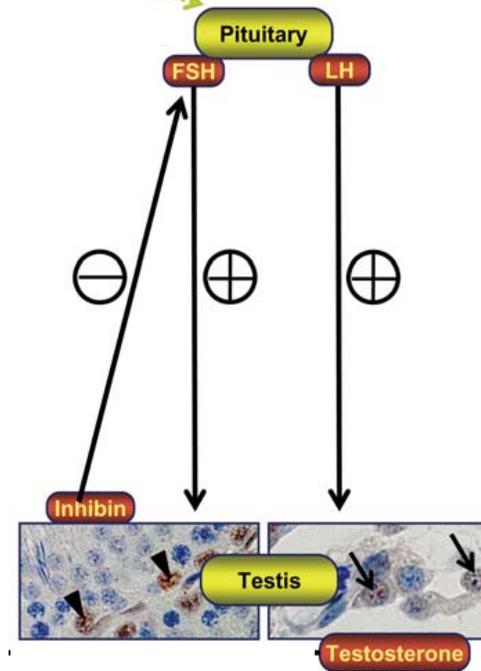
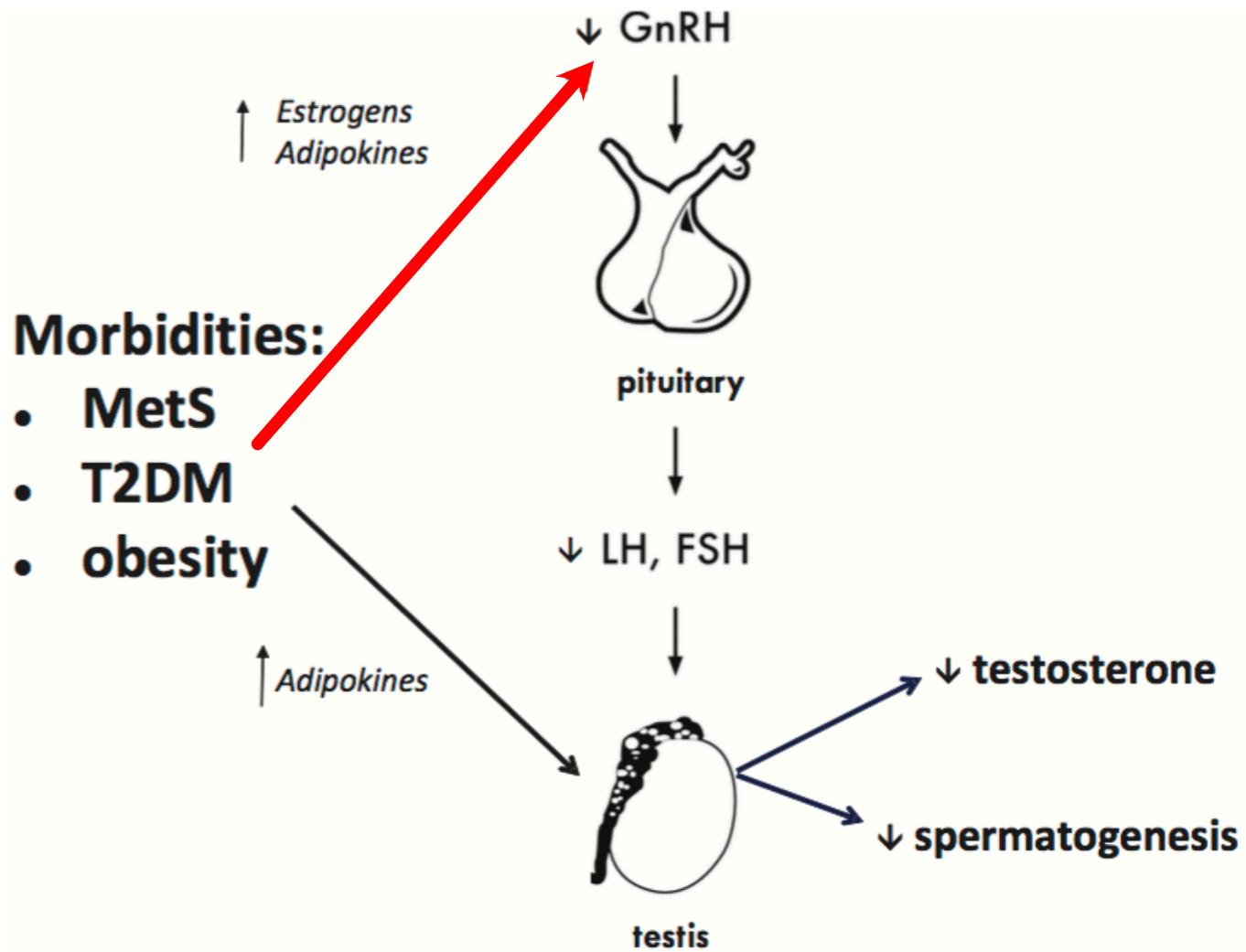
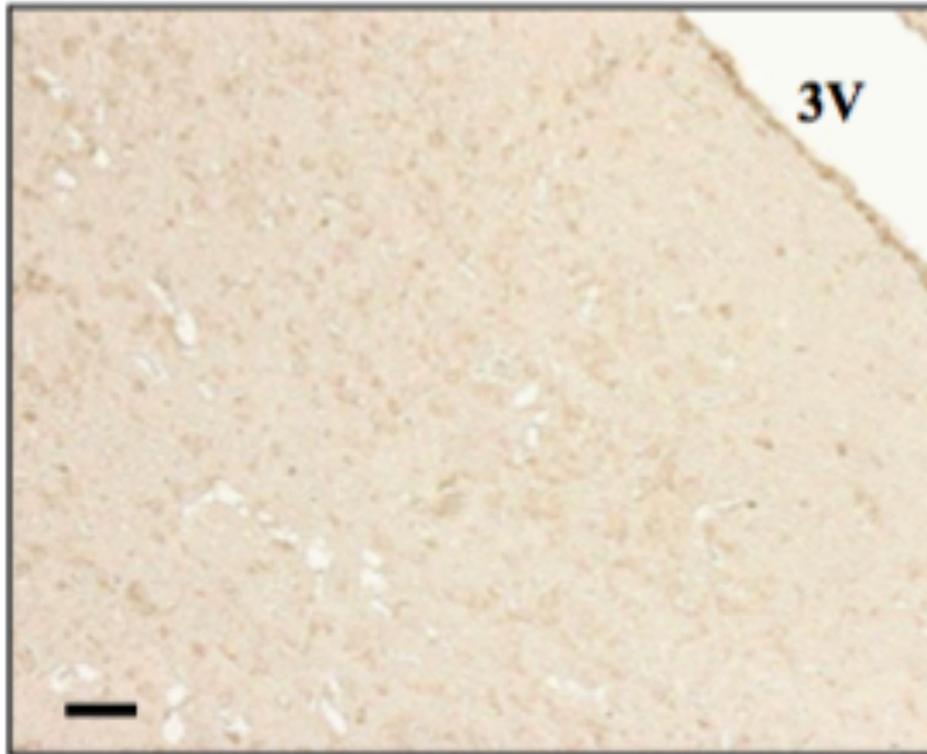


Figure 1. Proposed model of interaction between metabolic syndrome and testicular dysfunction.

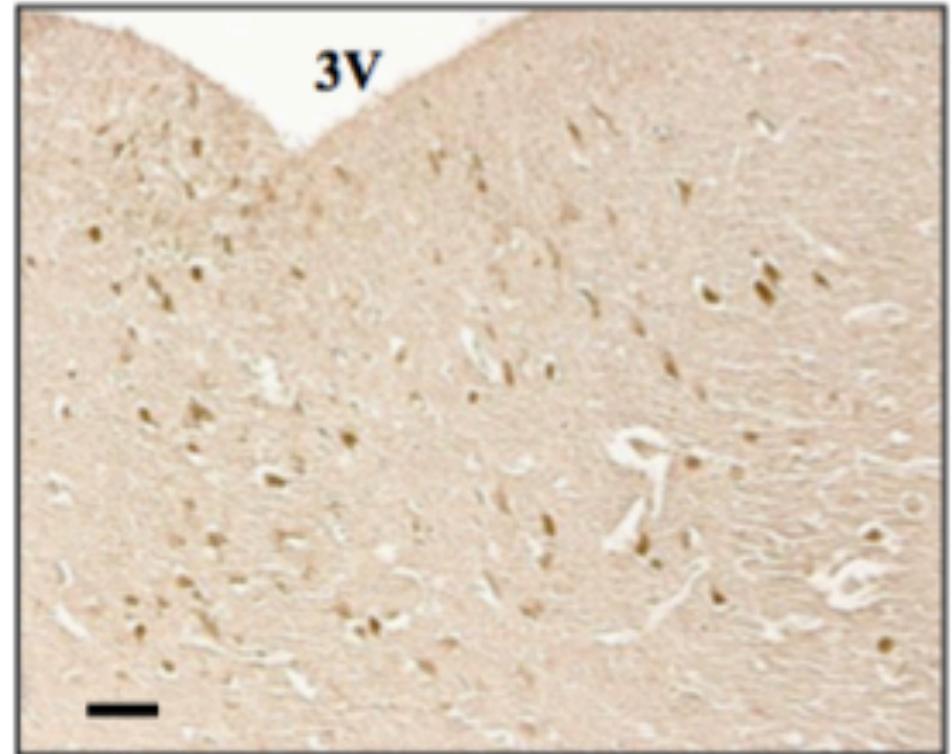




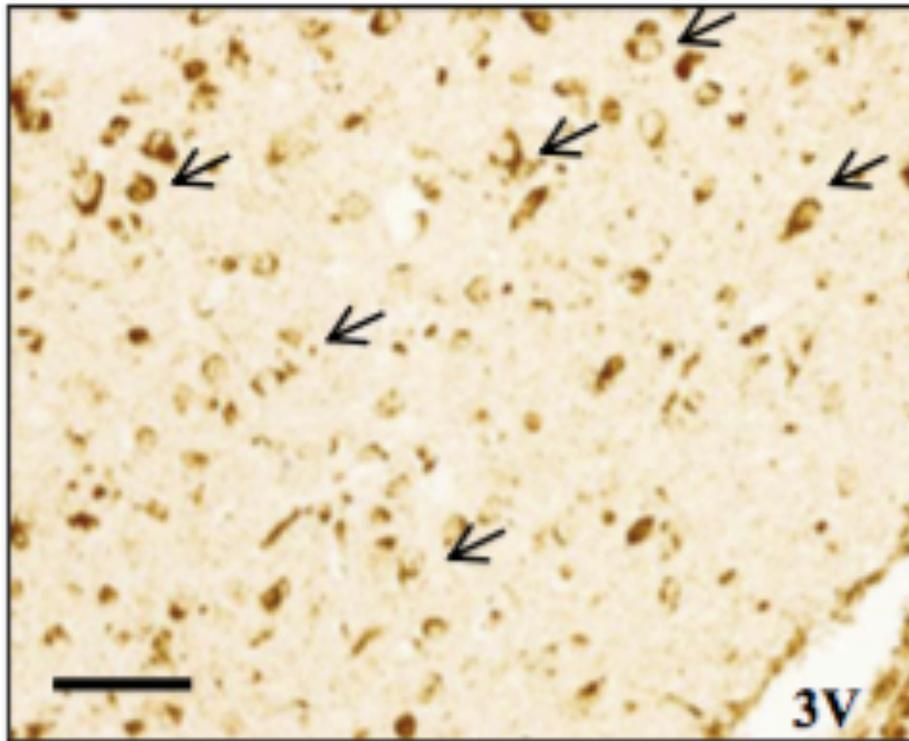
**(G) RD, IL-6**



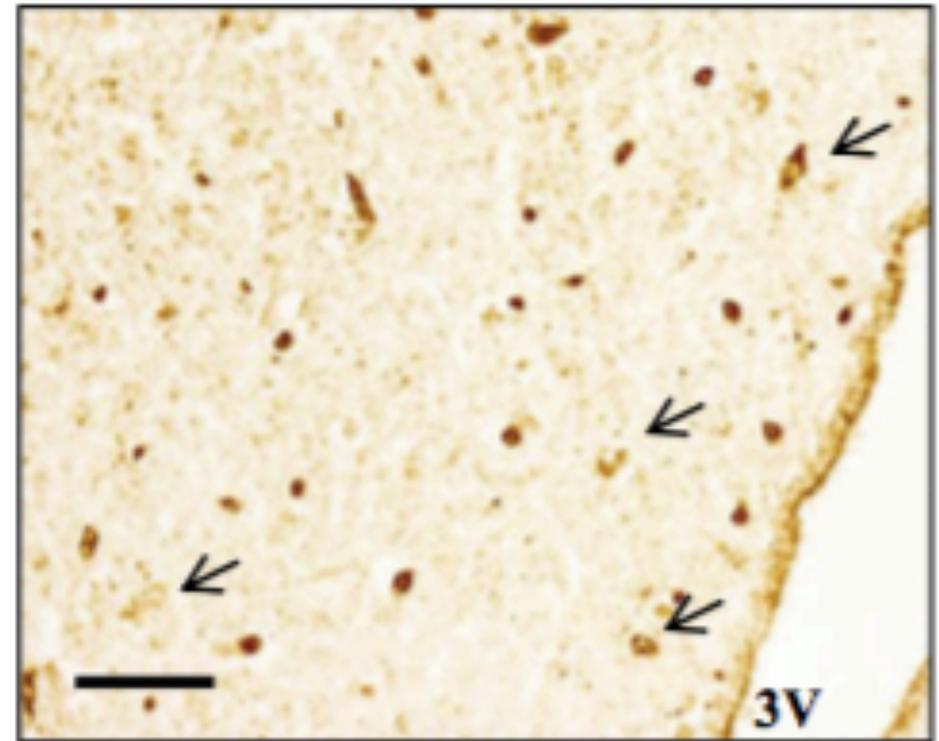
**(H) HFD, IL-6**



**(A) RD, KISS1R**



**(B) HFD, KISS1R**

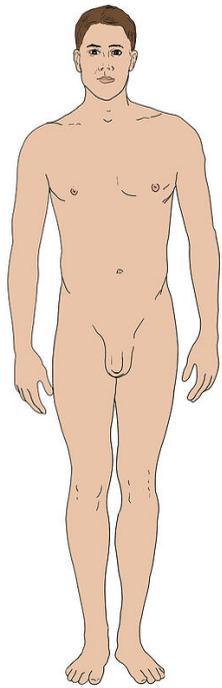




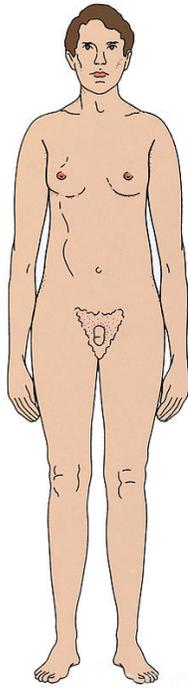
# When?

When do we have to treat hypogonadism?

# Hypogonadotropic hypogonadism



Healthy Male



Kallmann's syndrome

- Always
- Induce puberty
- Treat hypogonadism
- Treat co-morbidities
- Treat infertility

# Genotype of hypogonadotropic hypogonadism

**Table 1 | Genes implicated in CHH**

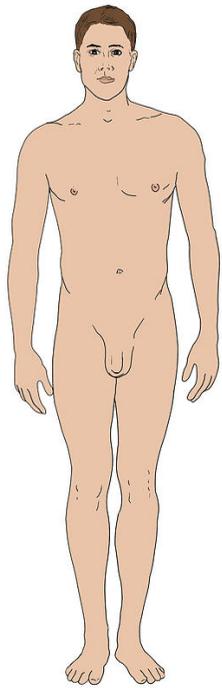
Gene	OMIM	CTO	CHH phenotypes			Overlapping syndromes										
			KS	CHH	CHH reversal	CPHD	CPHD + SOD	WS	CHARGE	HS	SHFM	D-WS	MGS	PEPNS	GHS	
KAL1 (ANOS1)	300836	✓	✓	×	✓	×	×	×	×	×	×	×	×	×	×	×
SEMA3A	614897	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×
SOX10	602229	×	✓	×	×	×	×	✓	×	×	×	×	×	×	×	×
OL14RD	606807	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×
HESX1	182230	×	✓	×	×	✓	✓	×	×	×	×	×	×	×	×	×
FEZF1	613301	×	✓	×	×	×	×	×	×	×	×	×	×	×	×	×
FGFR1	147950	✓	✓	✓	✓	✓	✓	×	×	✓	✓	×	×	×	×	×
FGF8	612702	✓	✓	✓	×	✓	×	×	×	×	×	×	×	×	×	×
CHD7	612370	×	✓	✓	✓	×	×	×	×	✓	×	×	×	×	×	×
FGF17	603725	✓	✓	✓	×	×	×	×	×	×	×	✓	×	×	×	×
HS6ST1	614880	✓	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×
PROK2	610628	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×
PROKR2	147950	✓	✓	✓	✓	✓	×	×	×	×	×	×	✓	×	×	×
SEMA7A	607961	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×
WDR11	614858	✓	✓	✓	×	✓	×	×	×	×	×	×	×	×	×	×
NSMF	614838	✓	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×
AXL	109135	×	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×
GNRH1	614841	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	×
GNRHR	146110	✓	×	✓	✓	×	×	×	×	×	×	×	×	×	×	×
KISS1	614842	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	×
KISS1R	614837	✓	×	✓	×	×	×	×	×	×	×	×	×	×	×	×
TAC3	614839	✓	×	✓	✓	×	×	×	×	×	×	×	×	×	×	×
TACR3	614840	✓	×	✓	✓	×	×	×	×	×	×	×	×	×	×	×
LEP	614962	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	×
LEPR	614963	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	×
PCSK1	162150	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	×
DMXL2	616113	×	×	✓	×	×	×	×	×	×	×	×	×	✓	×	×
RNF216	609948	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	✓
OTUD4	611744	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	✓
PNPLA6	603197	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	✓
NROB1	300200	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	×

Abbreviations: CHH, congenital hypogonadotropic hypogonadism; CHARGE, coloboma, heart defects, atresia of choanae, retardation of growth and/or development, genital and/or urinary defects, ear anomalies or deafness; CPHD, combined pituitary hormone deficiency; CTO, contributes to oligogenicity; D-WS, Dandy-Walker syndrome; GHS, Gordon Holmes syndrome; HS, Hartsfield syndrome; KS, Kallmann syndrome; MGS, Morning Glory syndrome; OMIN, online Mendelian inheritance in man; PEPNS, polyendocrine deficiencies and polyneuropathies; SHFM, split-hand/foot malformation; SOD, septo-optic dysplasia; WS, Waardenburg syndrome.

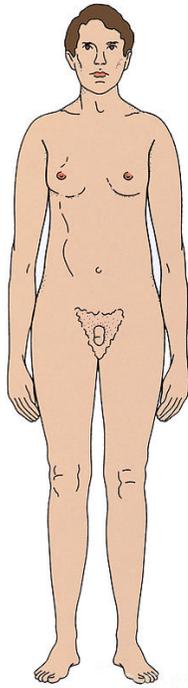
# Clinical spectrum of Kallmann's syndrome

- Cryptorchidism with or without micropenis
- Delayed puberty
- Hypogonadism
- Male infertility
- Anxiety and depression
- Hyposmia / anosmia
- Optic nerve hypoplasia
- Cleft lip and/or palate
- Dental agenesis
- Sensorineural deafness
- Congenital hearing impairment with or without pigmentation defects
- Bimanual synkinesia (mirror movements)
- Unilateral renal agenesis

# Hypergonadotropic hypogonadism



Healthy Male



Klinefelter's Syndrome

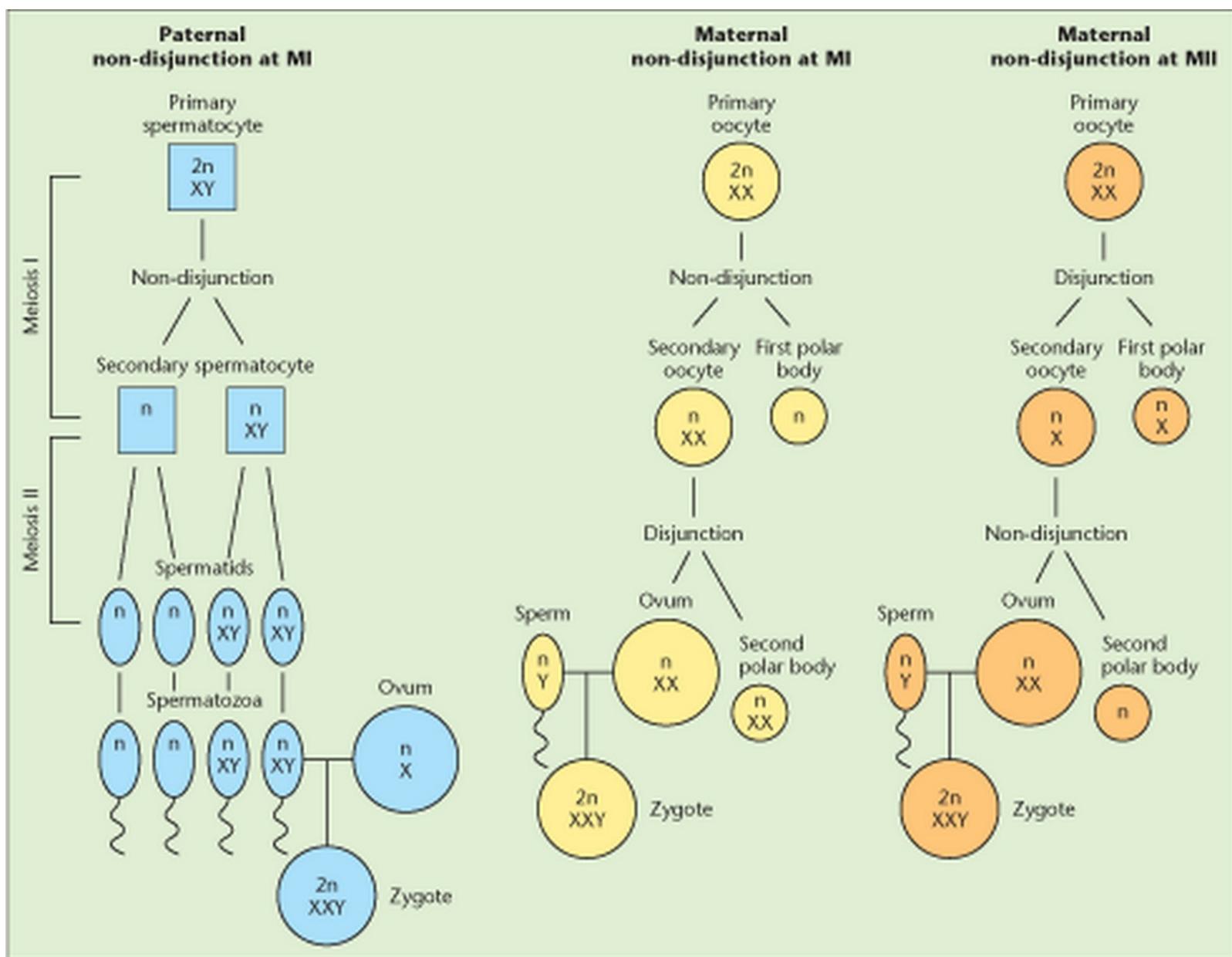
- Always
- Treat hypogonadism
- Treat co-morbidities
- Treat infertility

# Co-morbidities

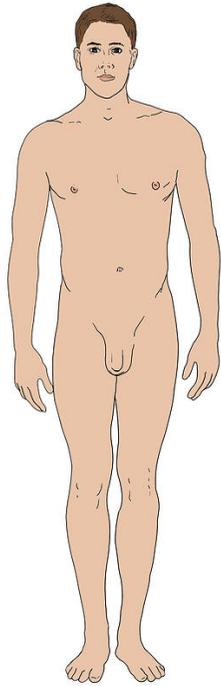
**Comorbidities in Klinefelter syndrome: prevalence and mortality**

	Incidence %	Reference	Mortality (SMR*)	Reference
Gynecomastia	38	(2)	–	–
Breast cancer	0.3	(e7)	29	(e7)
Thrombosis	4.7	(5)	8	(4)
Pulmonary embolism	2.3	(5)	6	(4)
Metabolic syndrome	44	(14)	–	–
Type 2 diabetes	10	(14)	6	(4)
Osteopenia	40	(18)	–	–
Osteoporosis	10	(18)	–	–
Hip fracture	?	–	39	(4)
Maldescended testes	27	(2)	–	–
Mediastinal tumors	0.4	(5)	–	–
Epilepsy	5.5	(5)	7	(4)
Mental retardation	4.2	(5)	–	–
Delayed verbal development	40	(19)	–	–
Language disorder	70 to 80	(21)	–	–
Legasthenia	50 to 70	(21)	–	–
Learning difficulties	75	(19)	–	–

\*SMR: standardized mortality rate, i.e. actual vs. predicted deaths (4)



# Late-onset hypogonadism



Aging male

- Be cautious!
- Combination of symptoms and low testosterone concentrations
- Treat co-morbidities

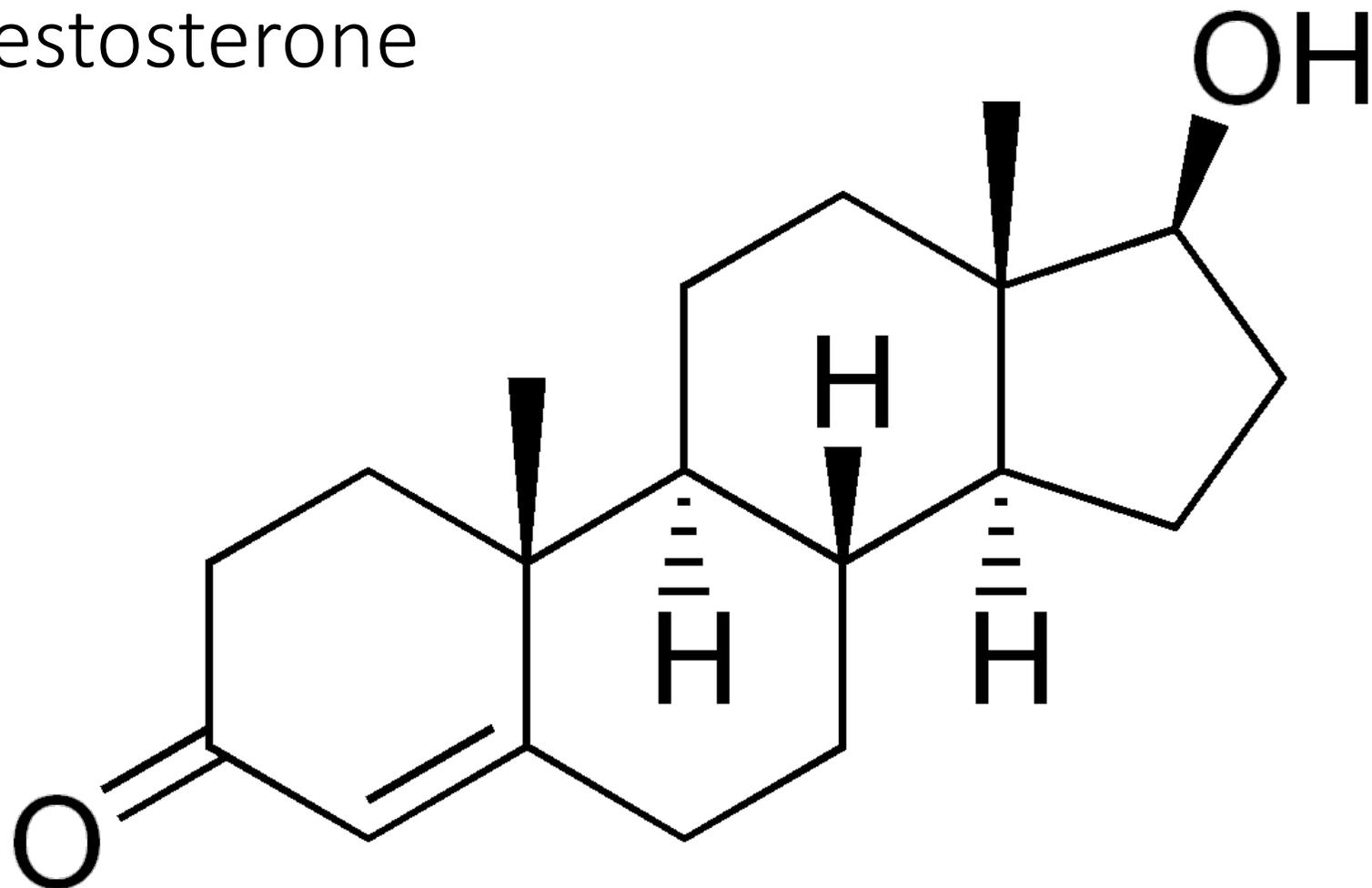
**Table 2. Identification and Prevalence of Symptoms Related to Testosterone in the Training Set.\***

Question Regarding Symptom	Evaluation Tool	Symptomatic Men	Asymptomatic Men	Symptom Prevalence	P Value	
					Total Testosterone	Free Testosterone
<b>Sexual symptoms</b>				%		
How frequently did you awaken with a full erection in the past month?	EMAS Sexual Function Questionnaire	≤1 time in the past mo	2–3 times in the past mo	39.9	0.007	<0.001
Were you able to get and keep an erection sufficient for sexual intercourse?	Massachusetts Male Aging Study	Never or sometimes	Usually or always	30.3	0.34	<0.001
How often did you think about sex?†	EMAS Sexual Function Questionnaire	2–3 times in the past mo	Once a week or more	27.5	0.048	<0.001
<b>Physical symptoms</b>						
During a typical day, did your health limit you in doing vigorous activity (e.g., running, lifting heavy objects, or participating in strenuous sports)? If so, how much?	SF-36	Limited	Limited a little or not at all	24.7	0.03	<0.001
During a typical day, did your health limit you in walking more than 1 km?	SF-36	Limited	Limited a little or not at all	6.7	0.01	<0.001
During a typical day, did your health limit you in bending, kneeling, or stooping?	SF-36	Limited	Limited a little or not at all	6.2	0.26	0.001
<b>Psychological symptom</b>						
Did you feel sad ("downhearted") during the past month?	SF-36	All or most of the time	Sometimes, a little, or none of the time	4.6	0.70	0.004
Have you felt a loss of energy in the past 2 wk, including today?	Beck Depression Inventory	Not enough energy to do very much or to do anything	As much energy as ever or less energy than usual	4.9	0.94	0.01
Do you feel more tired or fatigued than usual?	Beck Depression Inventory	Too tired to do a lot of things, as compared with usual	No major change in fatigue	5.5	0.30	<0.001

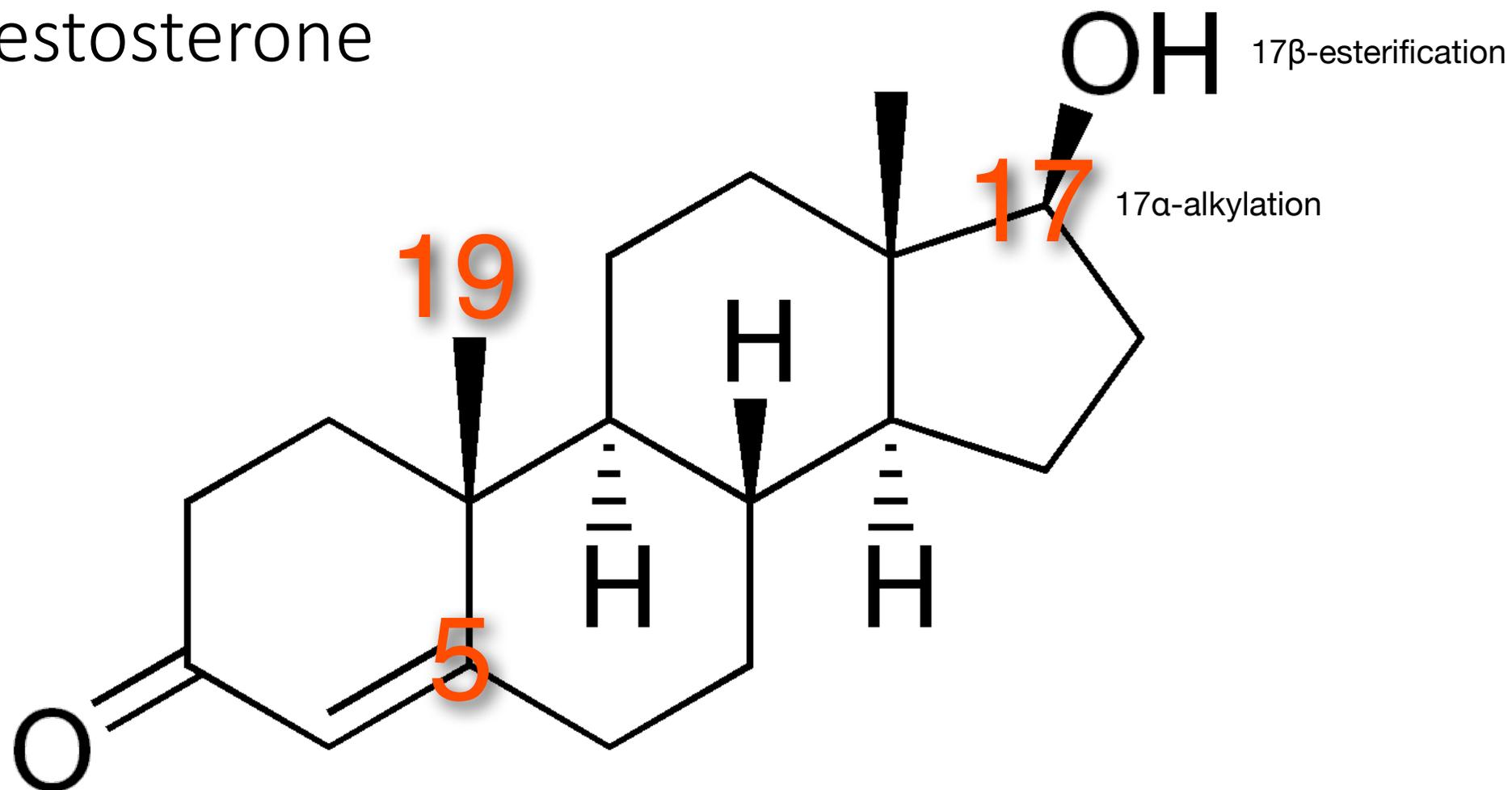
# How?

How do we treat hypogonadism?

Testosterone

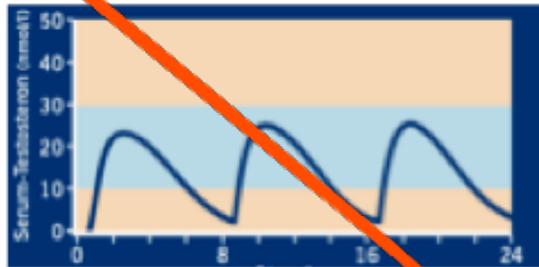


# Testosterone



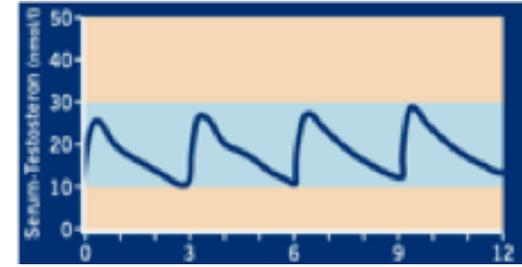
# Testosterone replacement therapy

Per os:  
3-4 tabs  
per day



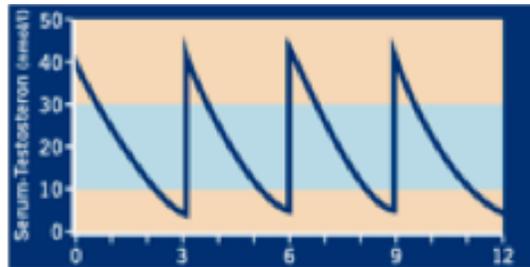
Hours

IM:  
every 10-14  
weeks



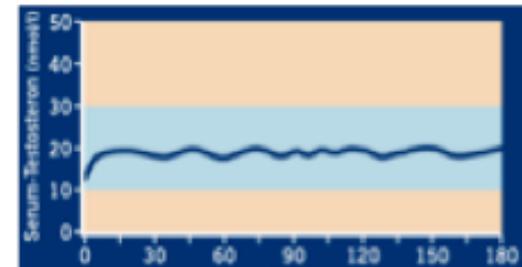
Months

IM:  
every 2-3  
weeks



Weeks

Gel:  
every day

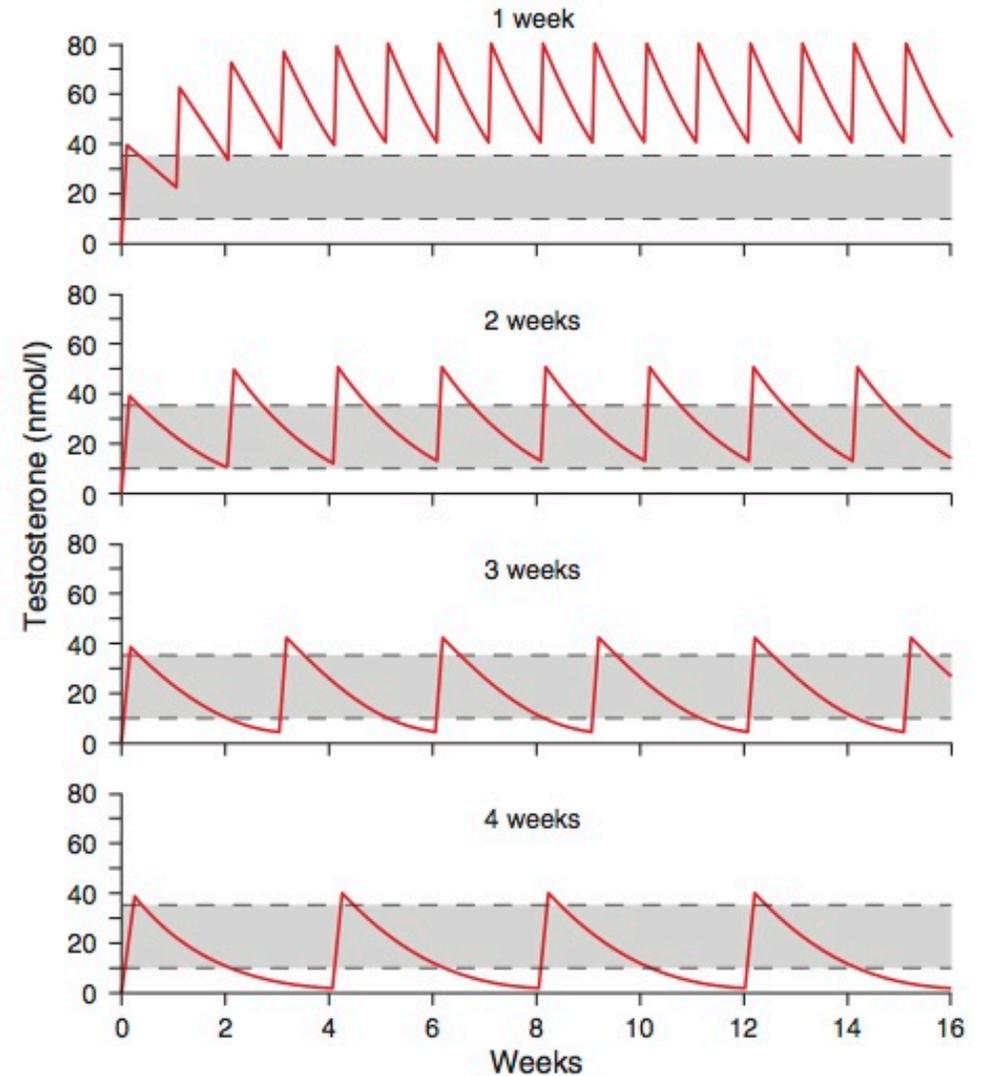


Hours

Patch:  
every day

# Testosterone replacement therapy

Intramuscular injection  
of 250 mg testosterone enanthate



	Preparation	Advantage	Disadvantage
	T pills	Effective	Liver toxicity
	T esters	Effective No daily administration Low cost	Deep IM injection Concentration fluctuations
	T esters (long active)	Effective	Large volume Commitment Lack of flexibility High cost
	T patches (non-scrotal)	Small fluctuations	Skin rash (30%) Poor adherence
	T gel	Small fluctuations	Poor efficacy Skin irritation Possible transfer High cost
	T buccal tabs		Twice a day Poor adherence
	T pellet	Every 3 - 6 months	Local anesthesia Infection, fibrosis
	T nasal gel	No transfer	Three times a day



# Expected benefits of T supplementation

## Good evidence

- Sexual characteristics (all HG)
- Glycemic control (MetS, T2DM)
- Lipid profile (all HG)
- Muscle strength (all HG)
- Fat mass (all HG)
- Bone mineral density (all HG)
- Cardiovascular disease (MetS, no CVD)
- Sexual function (severe HG)

## Poor / No evidence

- Glycemic control (all HG)
- BMI (all HG)
- Cardiovascular disease (known CVD)
- Sexual function (mild HG)



# Contra-indications

- Ca prostate
- PSA > 4 µg/l
- Ca breast
- Benign prostate hyperplasia, with obstruction (IPSS > 19)
- High hematocrit (> 50%)
- Sleep apnoea syndrome (untreated)
- Heart failure (uncontrolled)
- *Age per se is not a contra-indication*

# How?

How do we follow-up testosterone replacement therapy?

# Adverse effects

## **Proved**

- Liver toxicity
- Deterioration of benign prostate hyperplasia
- Mood disturbances
- Deterioration of sleep apnoea syndrome
- Polycythemia
- Acne / Gynecomastia (puberty)
- Closing of epiphyses (puberty)

## **Under investigation**

- Dyslipidemia
- Cardiovascular disease
- Benign prostate hyperplasia
- Ca prostate
- Aggressive behaviour



# Follow-up

## **Clinical parameters**

- History
  - Well-being
  - Sexual function
  - Sleep apnoea
- Examination
  - Virilization
  - Muscle strength
  - Blood pressure
  - Digital rectal examination

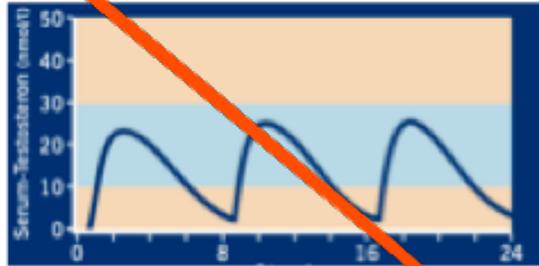
## **Laboratory parameters**

- Full blood count
- Liver enzymes
- Lipid profile
- PSA
- Testosterone, total
- (LH)
- SHBG
- (Bone mineral density)



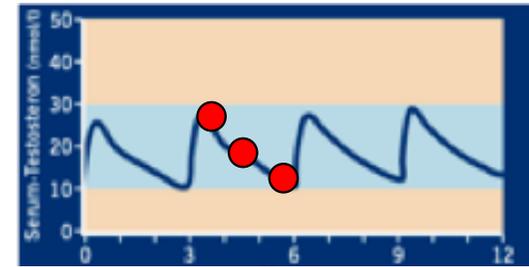
# Testosterone replacement therapy

Per os:  
3-4 tabs  
per day



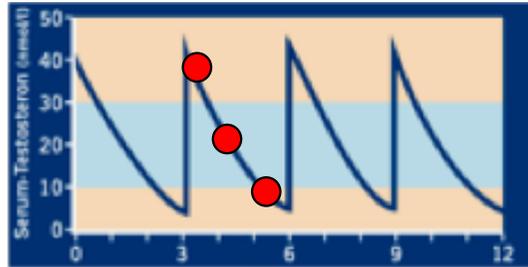
Hours

IM:  
every 10-14  
weeks



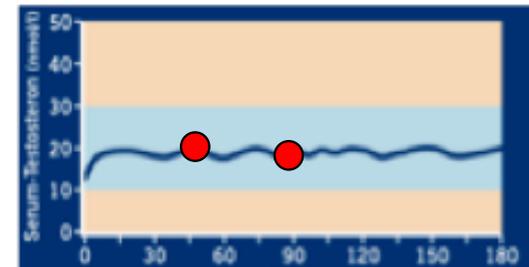
Months

IM:  
every 2-3  
weeks



Weeks

Gel:  
every day



Hours

Patch:  
every day

*The* NEW ENGLAND  
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## Effects of Testosterone Treatment in Older Men

P.J. Snyder, S. Bhasin, G.R. Cunningham, A.M. Matsumoto, A.J. Stephens-Shields, J.A. Cauley, T.M. Gill, E. Barrett-Connor, R.S. Swerdloff, C. Wang, K.E. Ensrud, C.E. Lewis, J.T. Farrar, D. Cella, R.C. Rosen, M. Pahor, J.P. Crandall, M.E. Molitch, D. Cifelli, D. Dougar, L. Fluharty, S.M. Resnick, T.W. Storer, S. Anton, S. Basaria, S.J. Diem, X. Hou, E.R. Mohler III, J.K. Parsons, N.K. Wenger, B. Zeldow, J.R. Landis, and S.S. Ellenberg,  
for the Testosterone Trials Investigators\*

**Table 4. Adverse Events during the First Year (Treatment Period) of the Testosterone Trials.\***

Event	Placebo	Testosterone
	(N = 394)	(N = 394)
	<i>no. of participants</i>	
Prostate-related event		
Increase in PSA level by $\geq 1.0$ ng/ml	8	23
Prostate cancer	0	1
IPSS $>19$ <sup>†</sup>	26	27
Hemoglobin $\geq 17.5$ g/dl	0	7
Cardiovascular event <sup>‡</sup>		
Myocardial infarction (definite or probable)	1	2
Stroke (definite or probable)	5	5
Death from cardiovascular causes	1	0
Myocardial infarction, stroke, or death from cardiovascular causes	7	7
Serious adverse events		
Death	7	3
Hospitalization	78	68
Other <sup>§</sup>	6	7

# What?

What else can we do to treat hypogonadism?

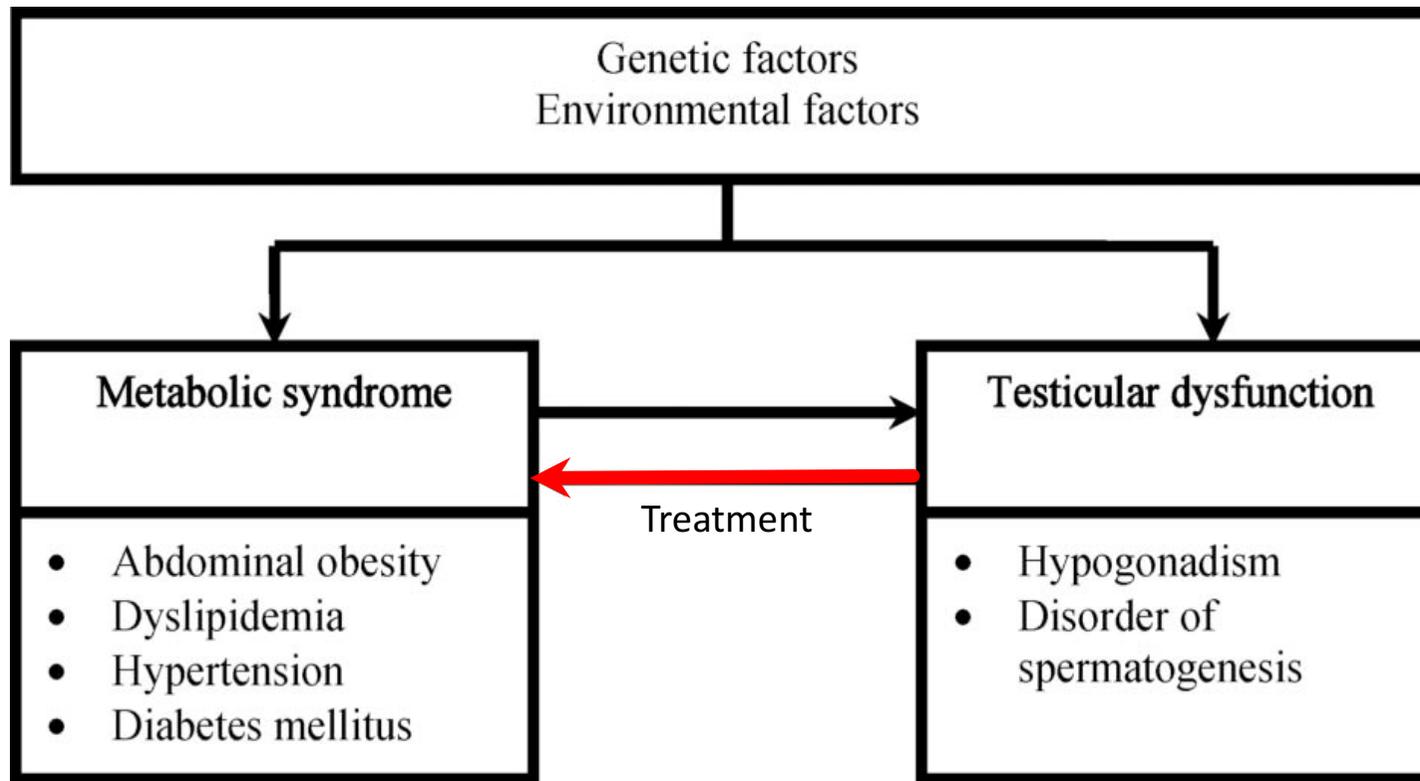
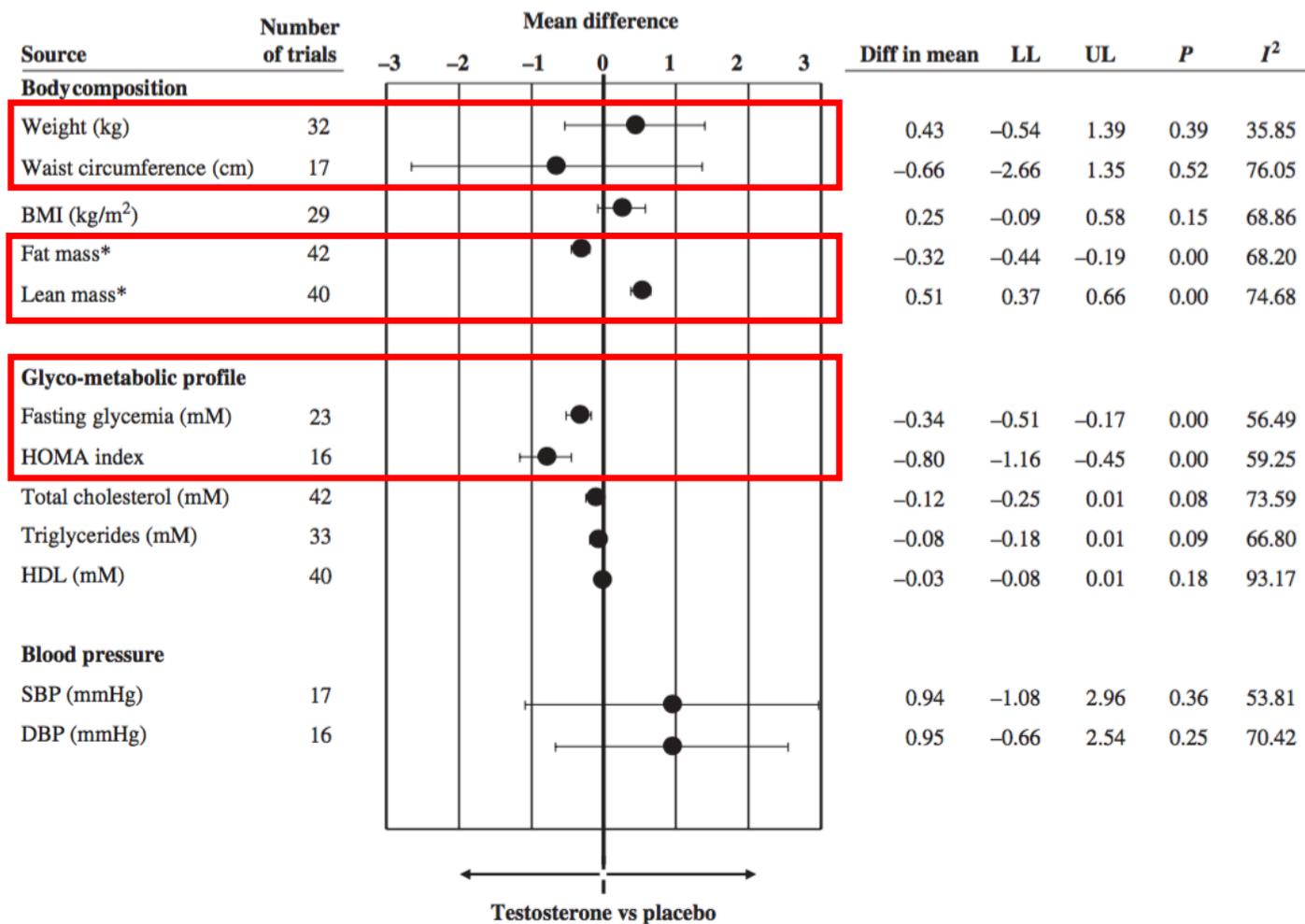


Figure 1. Proposed model of interaction between metabolic syndrome and testicular dysfunction.



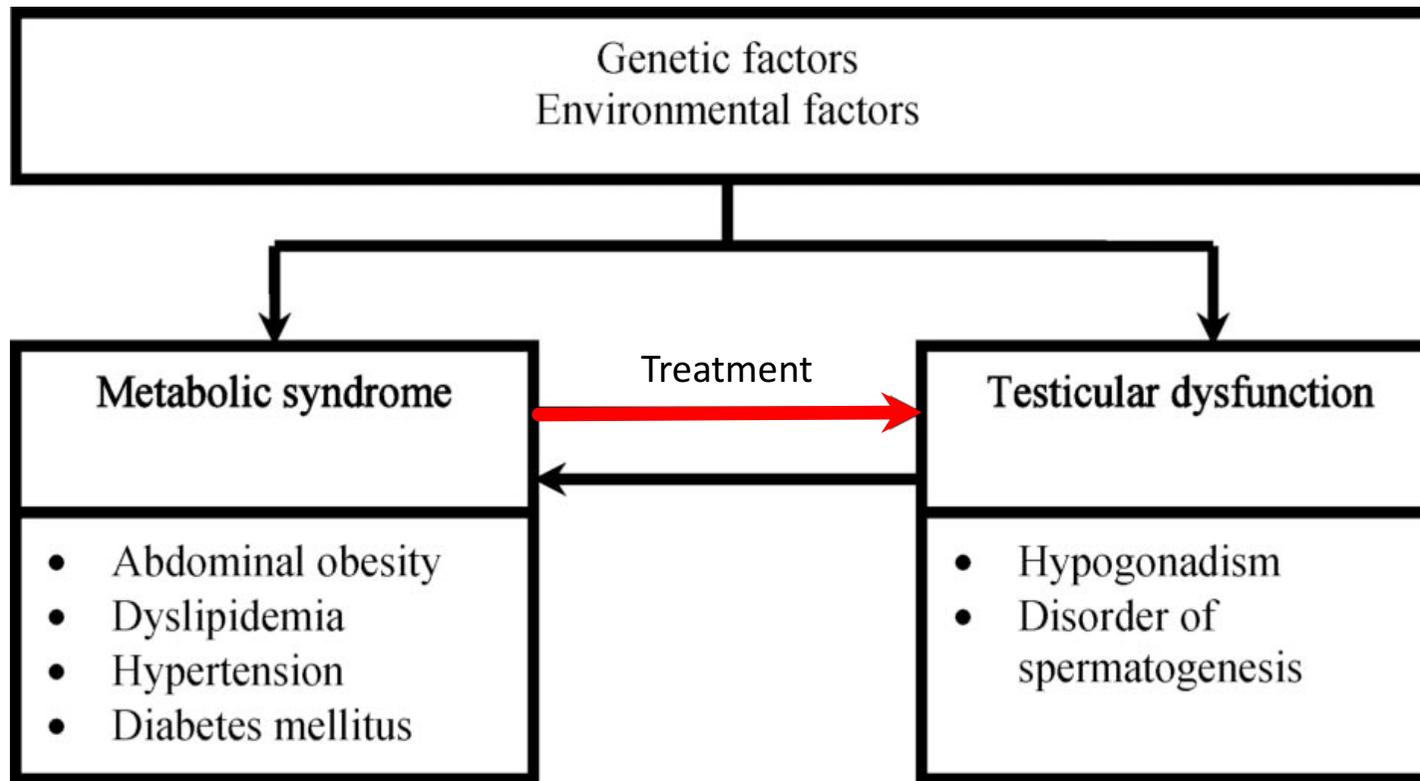
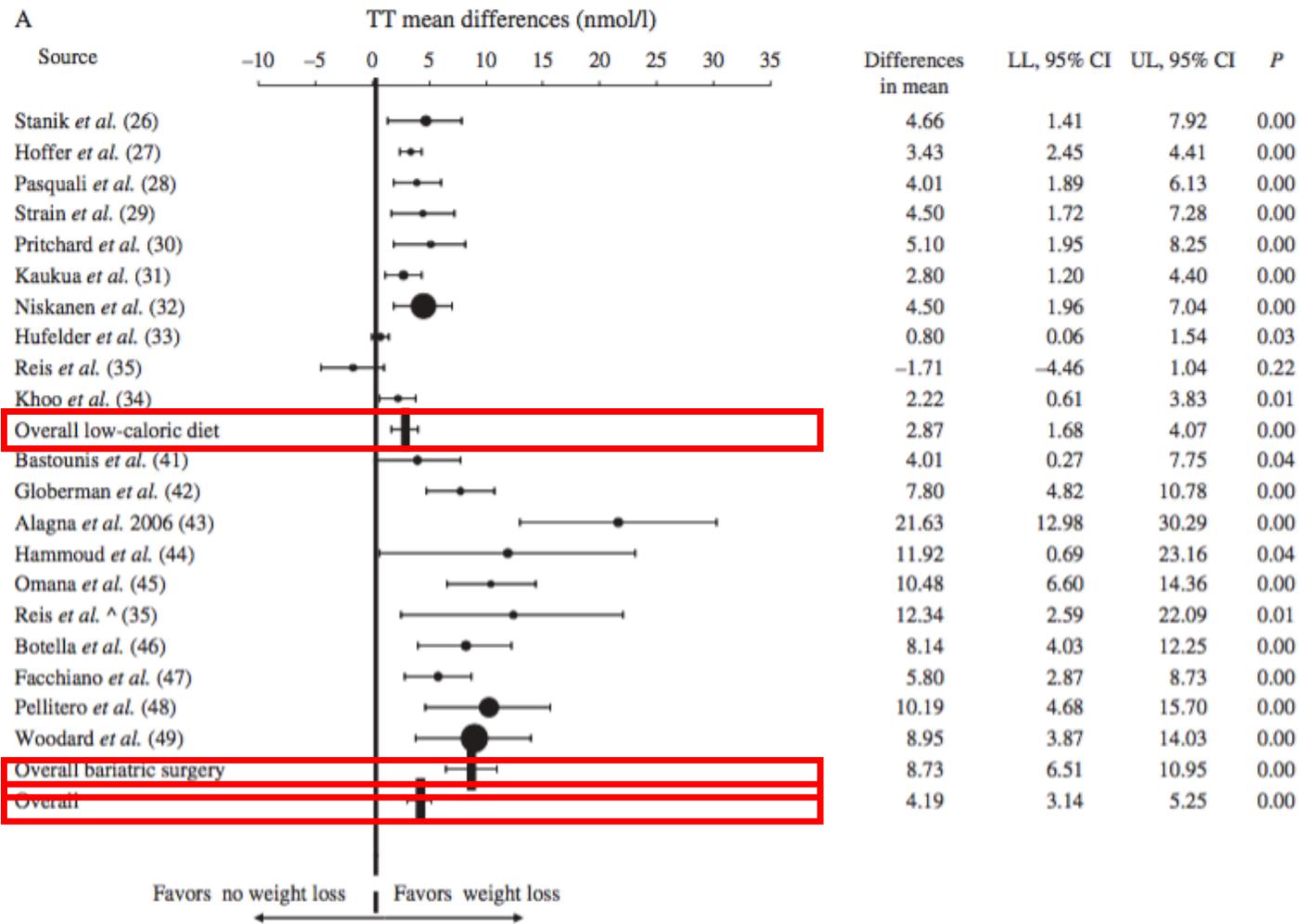
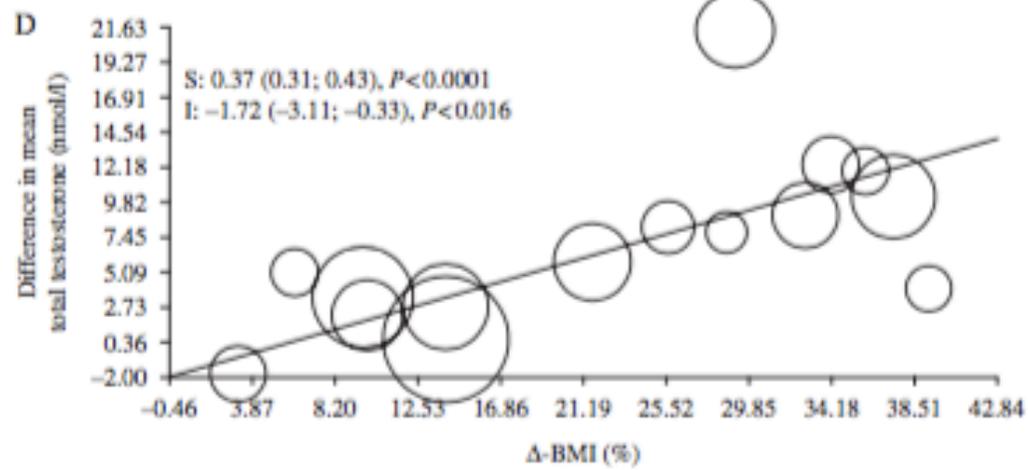
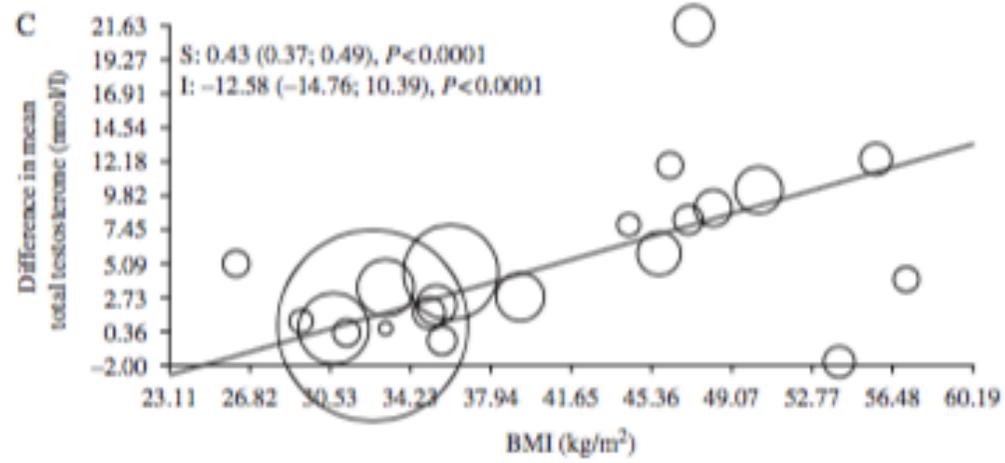


Figure 1. Proposed model of interaction between metabolic syndrome and testicular dysfunction.





# How?

How do we summarize?

# What we will do

- Provide current concepts of male hypogonadism
- Discuss practical issues of testosterone supplementation
- Emerge the role of life-style interventions on the management of male hypogonadism

# Hypogonadism

- Definition

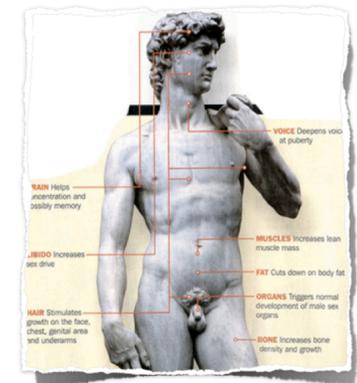
- Clinical picture

## Testicular function



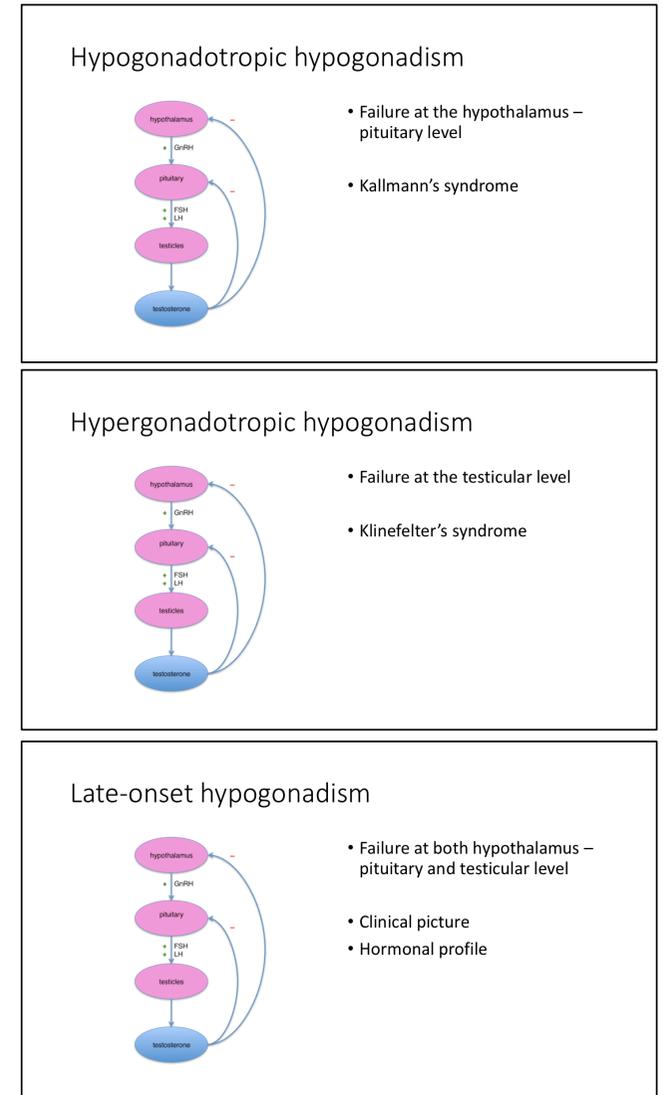
- Failure of endocrine function
  - Low serum testosterone
  - Male hypogonadism
- Failure of exocrine function
  - Poor sperm quality
  - Male infertility

## Testosterone actions



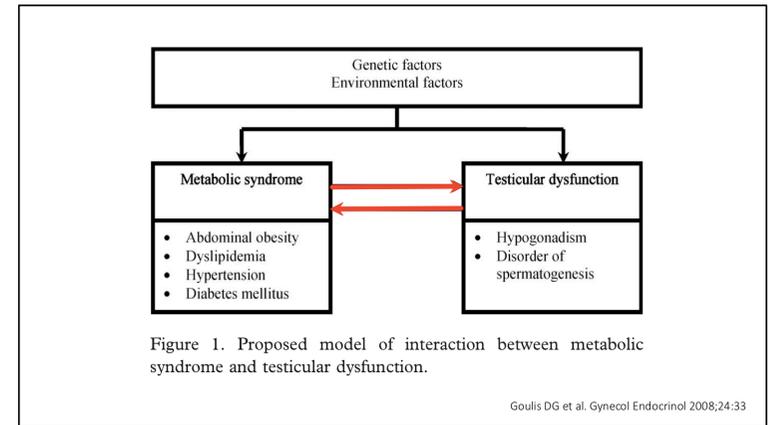
# Types of hypogonadism

- Hypogonadotropic hypogonadism
- Hypergonadotropic hypogonadism
- Late-onset hypogonadism



# Pathophysiology

- Connection of hypogonadism to obesity



# T replacement therapy

- Contra-indications

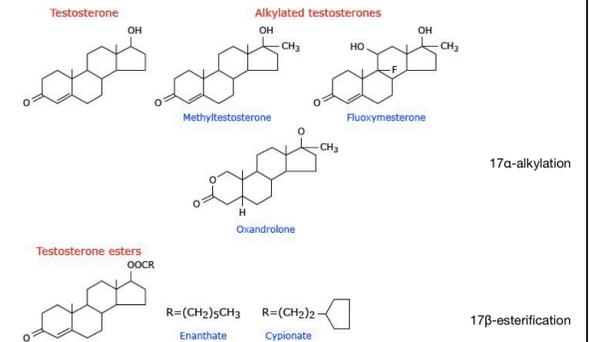
- Preparations

- Routes of administration

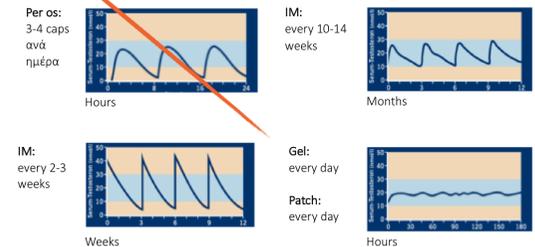
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- High hematocrit (> 50%)
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- Heart failure (uncontrolled)
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## Testosterone replacement therapy



# T replacement therapy

- Regimen comparison
- Follow-up
- Adverse effects
- Cardiovascular disease

Preparation	Advantage	Disadvantage
✗ T pills	Effective	Liver toxicity
✓ Testers	Effective No daily administration Low cost	Deep IM injection Concentration fluctuations
✓ Testers (long active)	Effective	Large volume Commitment Lack of flexibility High cost
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## Follow-up



### Clinical parameters

- History
  - Well-being
  - Sexual function
  - Sleep apnoea
- Examination
  - Virilization
  - Muscle strength
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### Laboratory parameters

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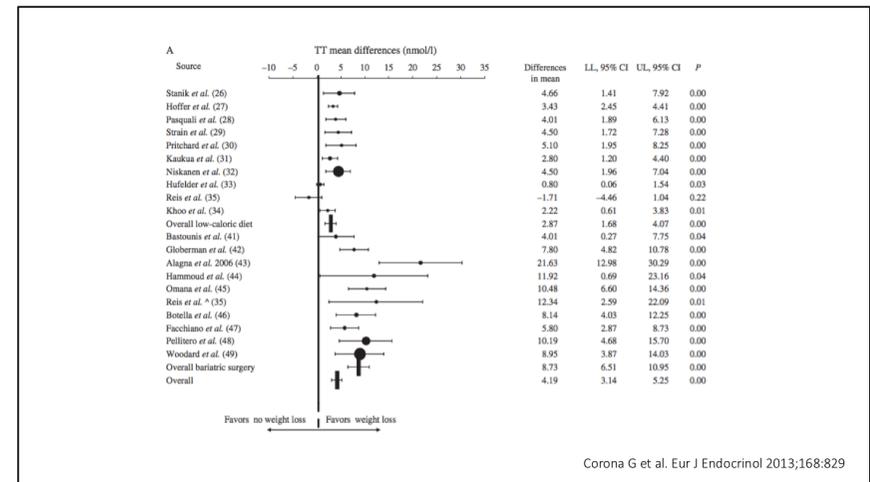
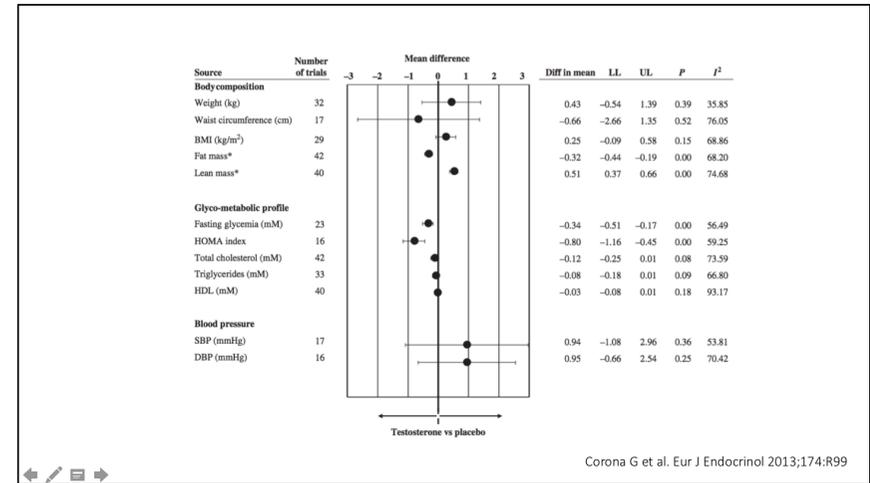
### Under investigation

- Dyslipidemia
- Cardiovascular disease
- Benign prostate hyperplasia
- Ca prostate
- Aggressive behaviour

# Medical nutrition therapy

- T supplementation improves metabolic syndrome parameters

- Weight loss improves serum T concentrations



# How?

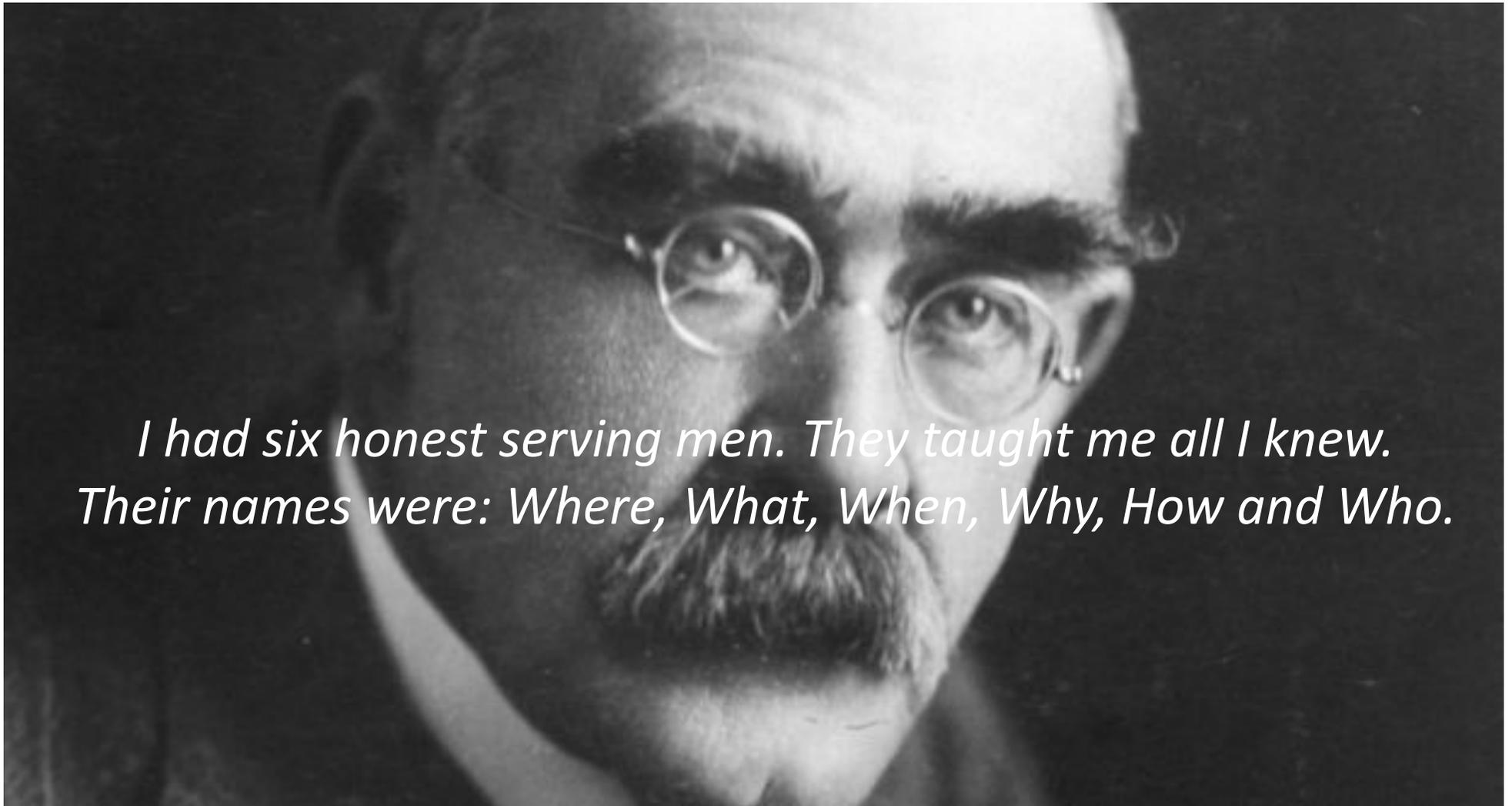
How do we conclude?

# What do we know?

- TRT should be administered **only to men who are hypogonadal**, as evidenced by clinical symptoms and signs and subnormal serum testosterone concentration
- TRT can be administered whether the testosterone deficiency is due to hypergonadotropic or hypogonadotropic hypogonadism
- The principal goal of TRT is to restore the serum testosterone concentration within the normal range
- TRT is applied through T ester injections or transdermal preparations (gels and patches)

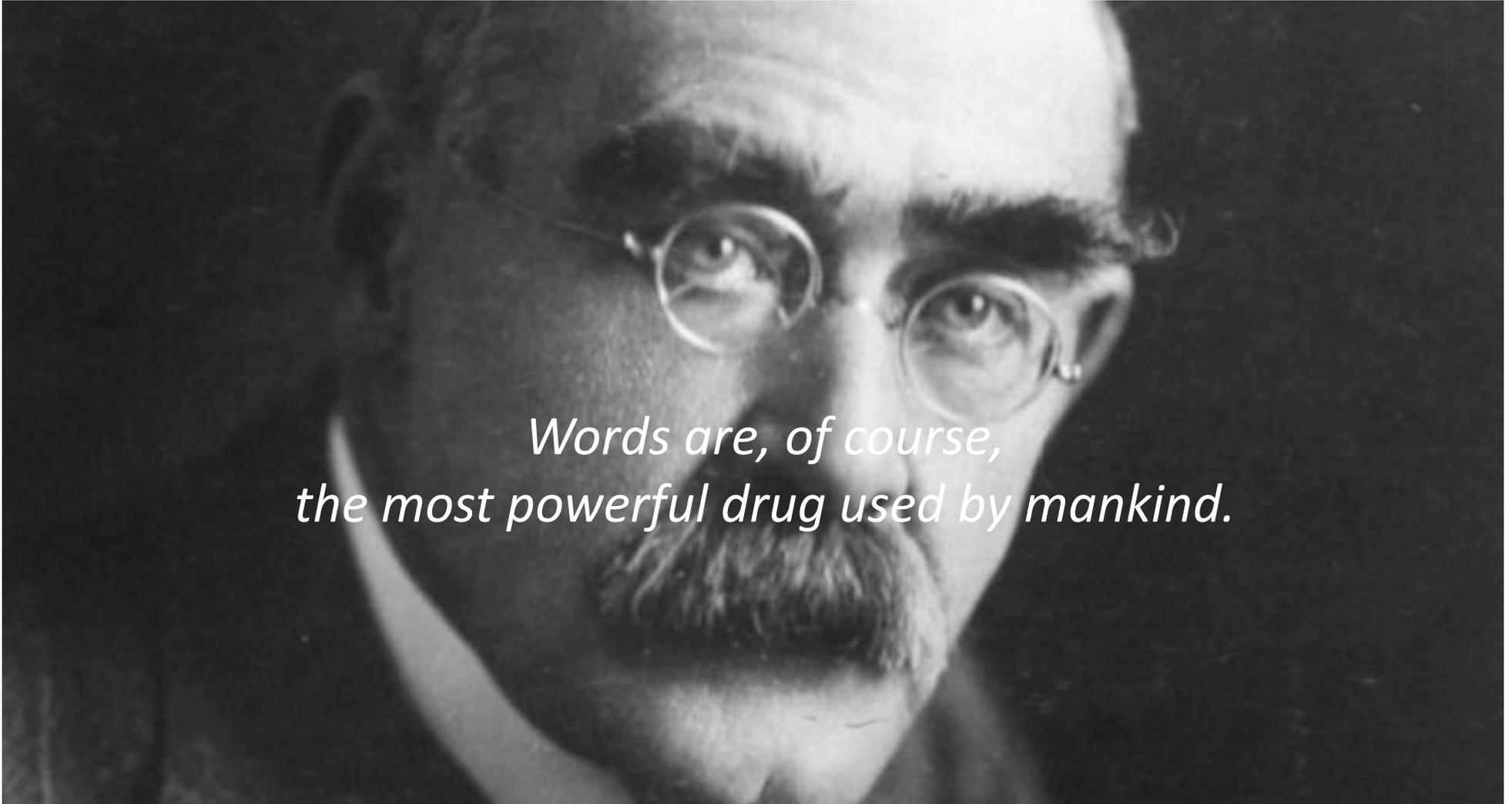
# What don't we know?

- If restoring the normal circadian rhythm of testosterone is important
- If we have to administer TRT to treat the decline in serum testosterone concentration that occurs with increasing frequency above 60 years of age (LOH)



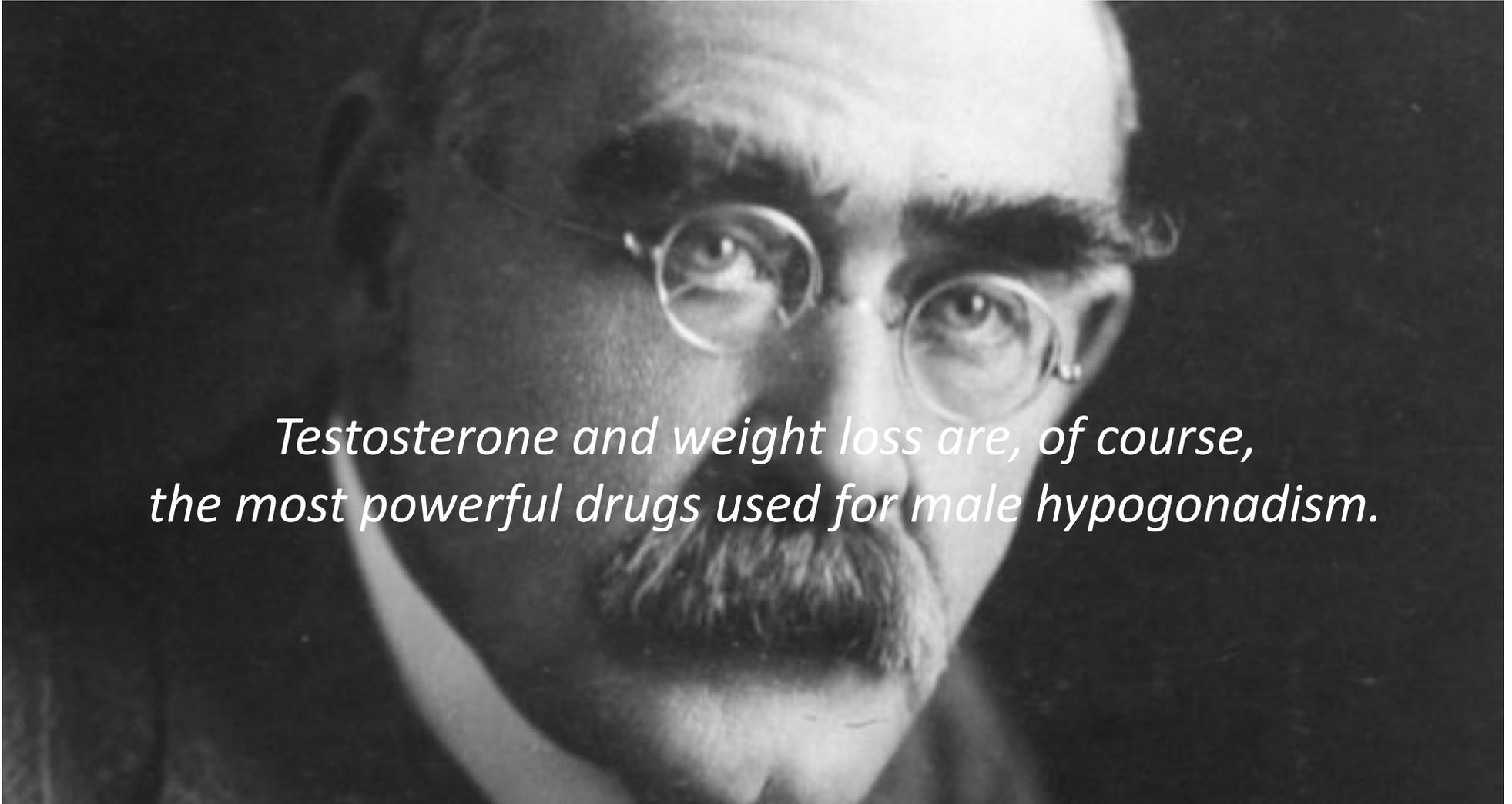
*I had six honest serving men. They taught me all I knew.  
Their names were: Where, What, When, Why, How and Who.*

Rudyard Kipling (1865 - 1936)

A black and white close-up portrait of Rudyard Kipling. He is wearing round-rimmed glasses and has a prominent mustache. The lighting is dramatic, with strong highlights on his forehead and nose, and deep shadows on the sides of his face. The background is dark and out of focus.

*Words are, of course,  
the most powerful drug used by mankind.*

Rudyard Kipling (1865 - 1936)

A black and white portrait of Rudyard Kipling, an elderly man with a prominent mustache and round glasses, looking directly at the camera. The background is dark and out of focus.

*Testosterone and weight loss are, of course,  
the most powerful drugs used for male hypogonadism.*

Rudyard Kipling (1865 - 1936)

## Unit of Reproductive Endocrinology

Associate professor D.G. Goulis

Professor emeritus J. Papadimas



Unit of Reproductive Endocrinology  
Department of Obstetrics and Gynecology  
Aristotle University of Thessaloniki  
Head: Professor G.F. Grimbizis

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