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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.

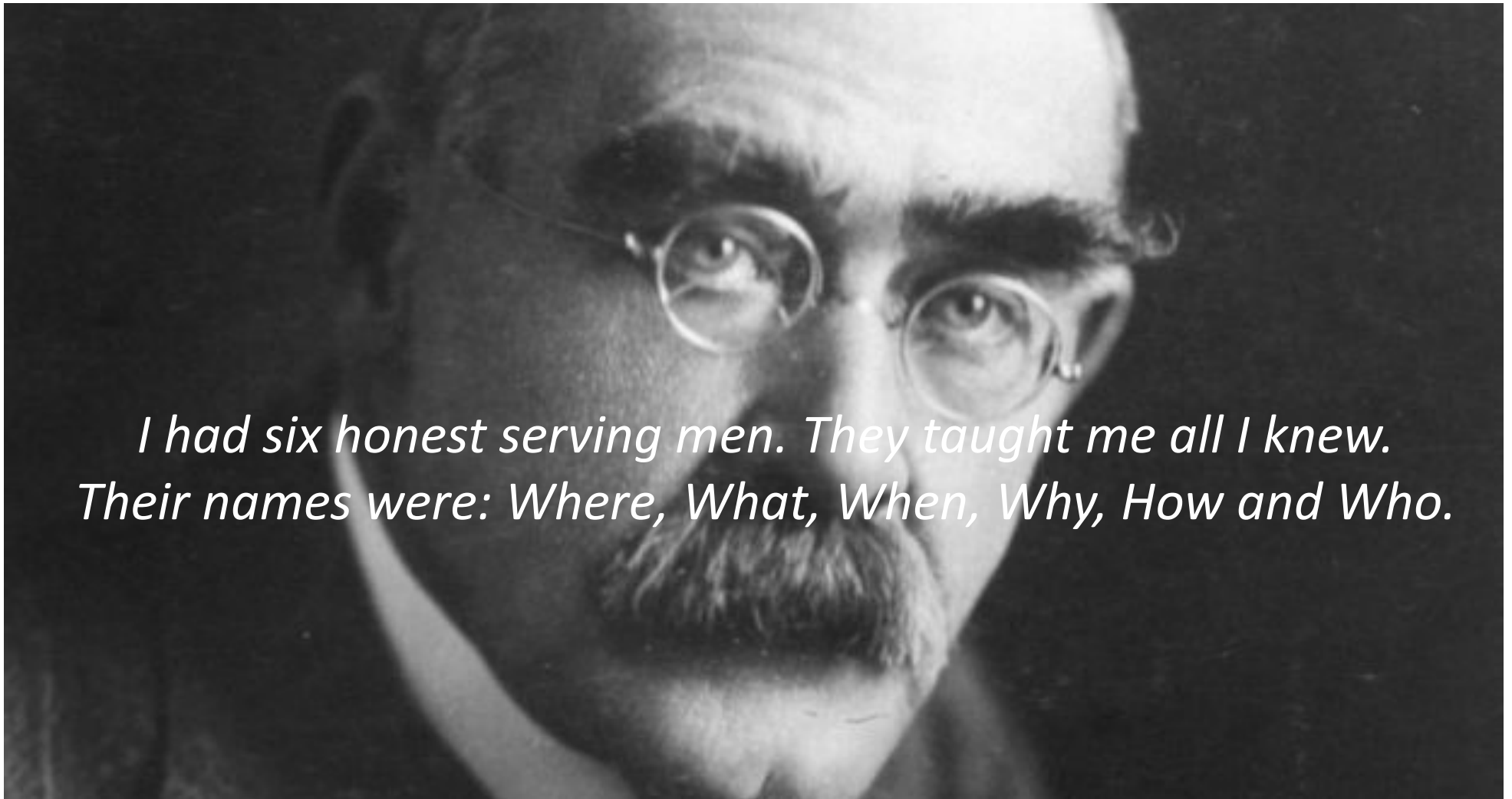
What we will do

- 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.*

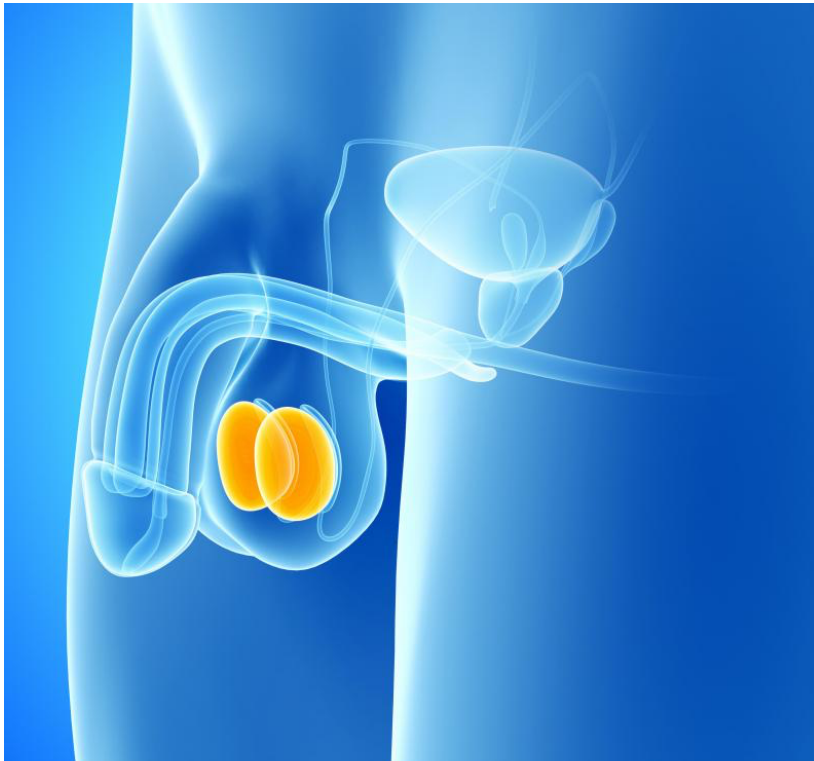
Rudyard Kipling (1865 - 1936)



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



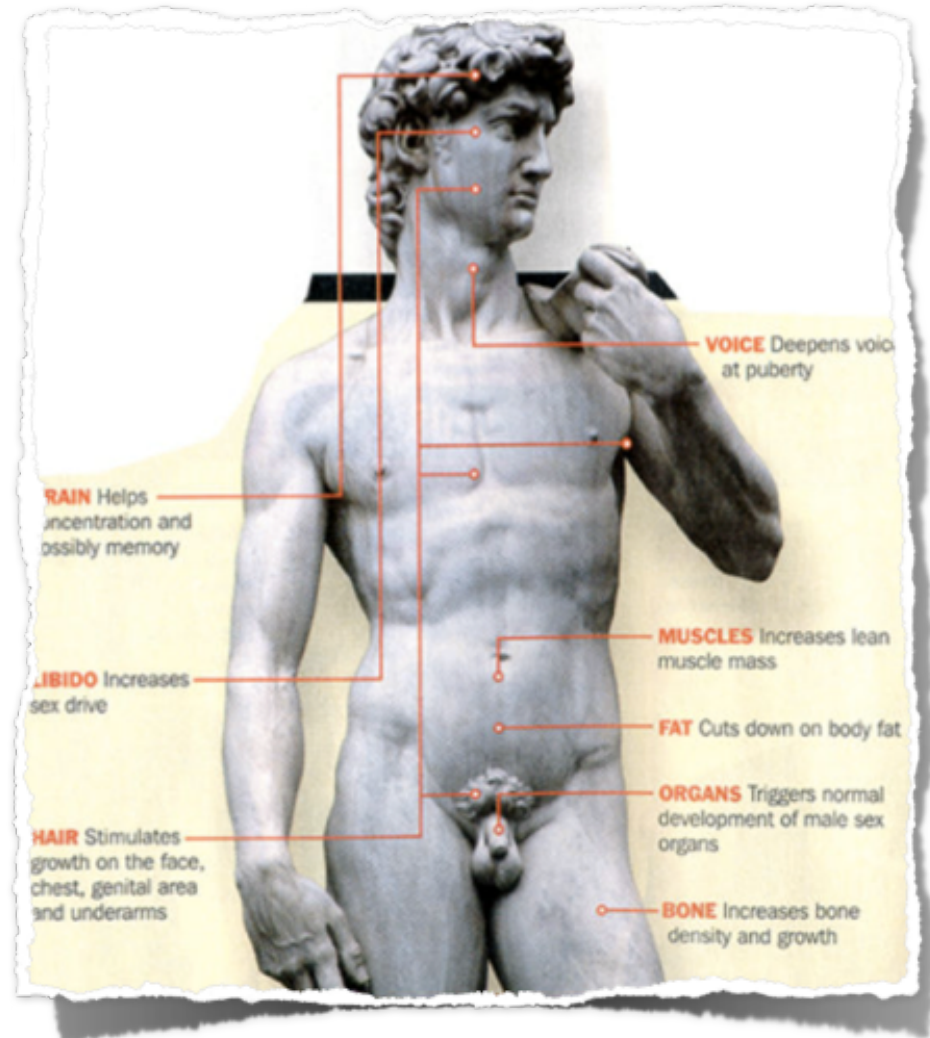
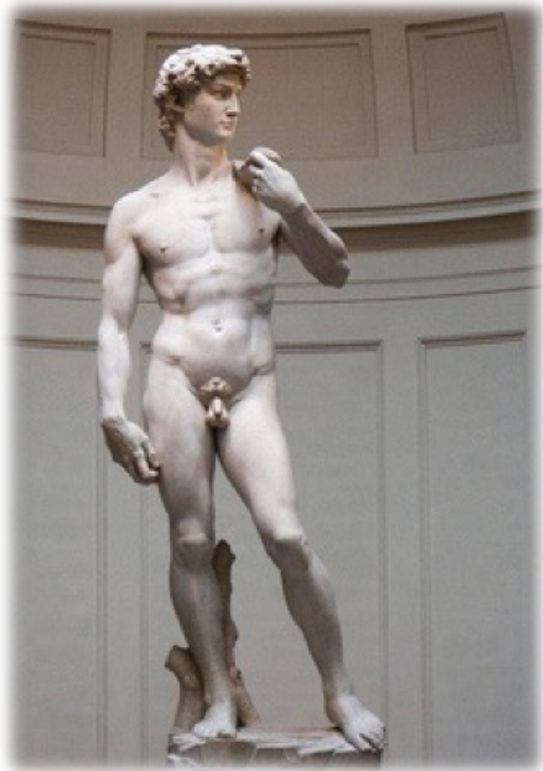
Infertility → Hypogonadism



What?

What is the clinical picture of male hypogonadism?

Testosterone actions





Clinical picture

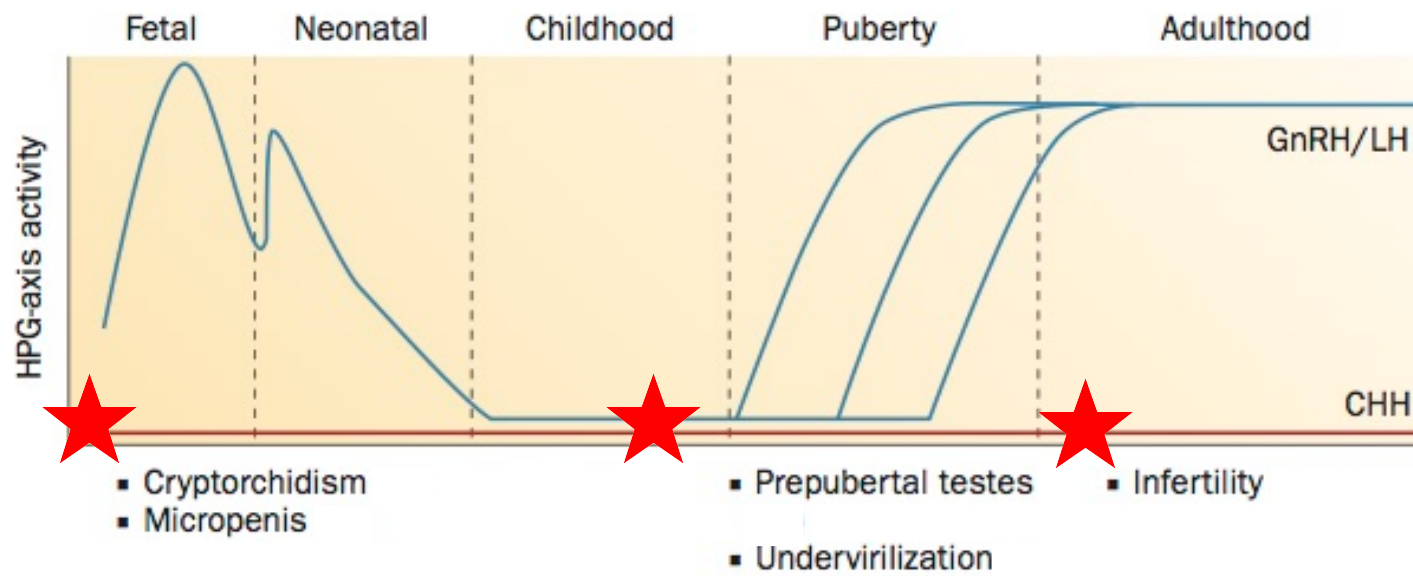
High specificity

- 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

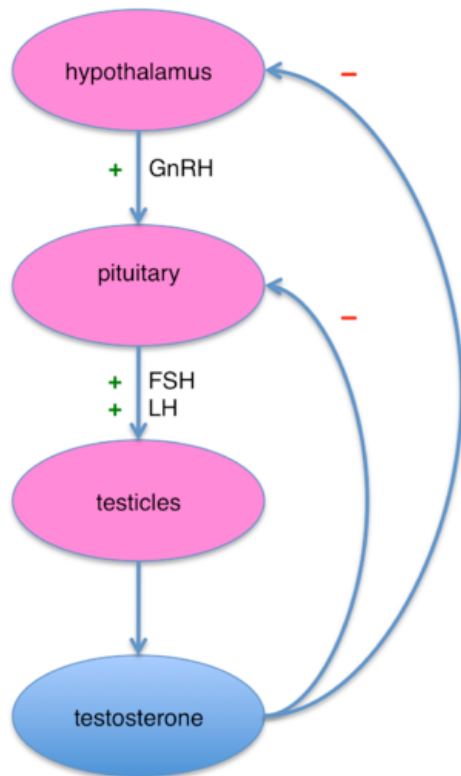
- Relative Risk (adjusted for age) for males with total T < 200 ng/dl in comparison to males with total T 400 - 600 ng/dl:
 - 1.93 for overall mortality
 - 3.30 for disease-specific mortality (cancer)
 - 1.93 for disease-specific mortality (cardiovascular disease)



What?

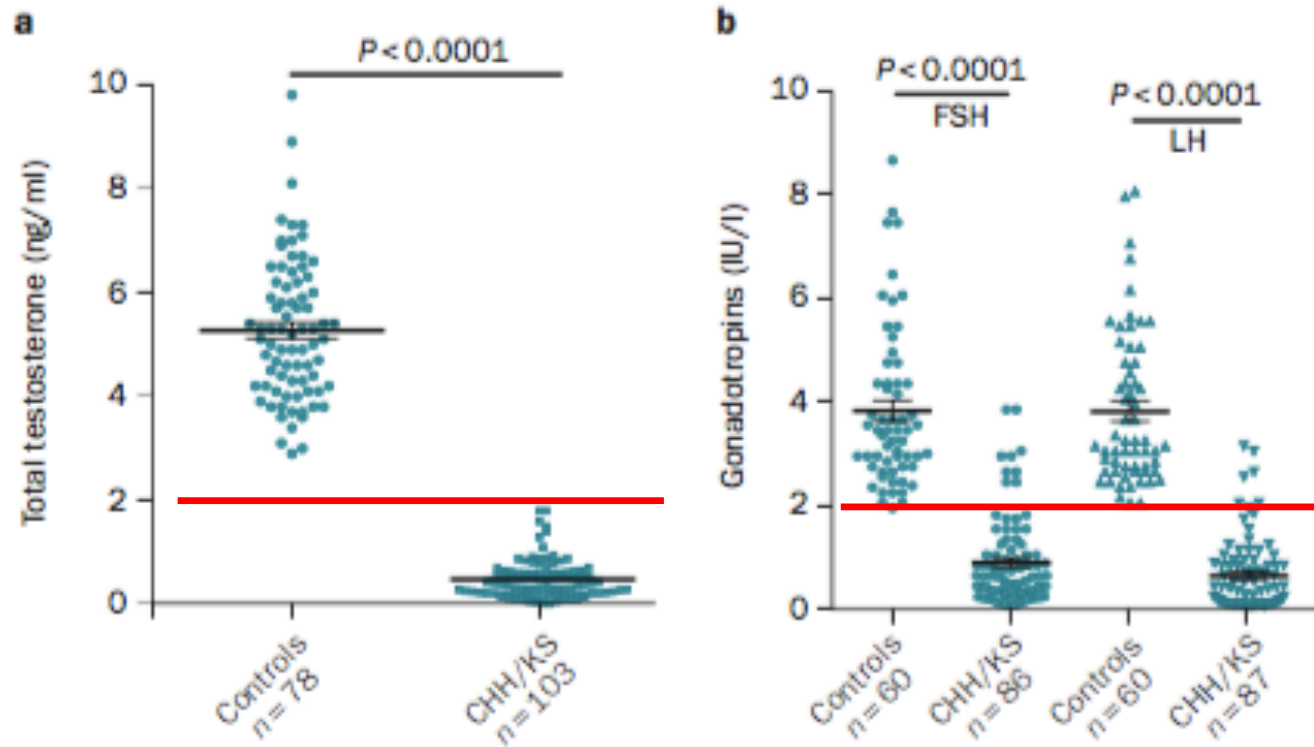
What are the types of hypogonadism?

Hypogonadotropic hypogonadism



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

Hormonal profile



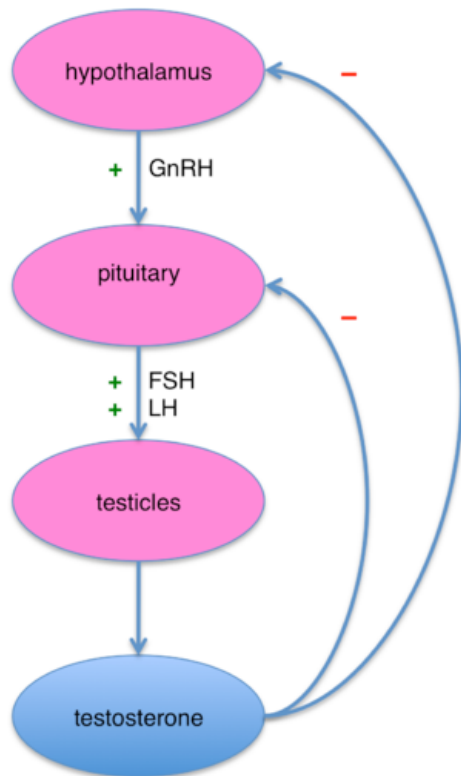
Trabado S et al. J Clin Endocrinol Metab 2014;99:E268
Young J. J Clin Endocrinol Metab 2012;97:707

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

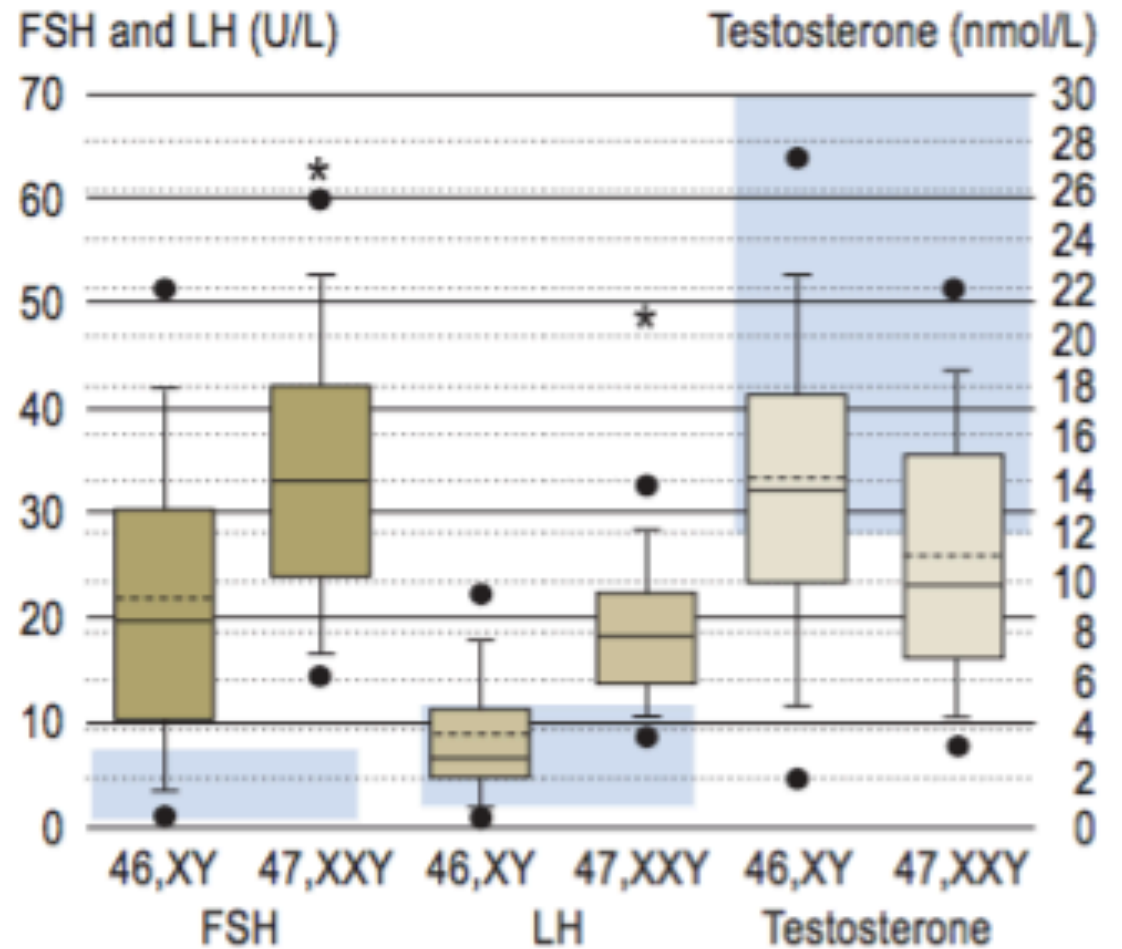
GnRH: gonadotropin-releasing hormone.

Hypergonadotropic hypogonadism



- Failure at the testicular level
- Klinefelter's syndrome

Hormonal profile

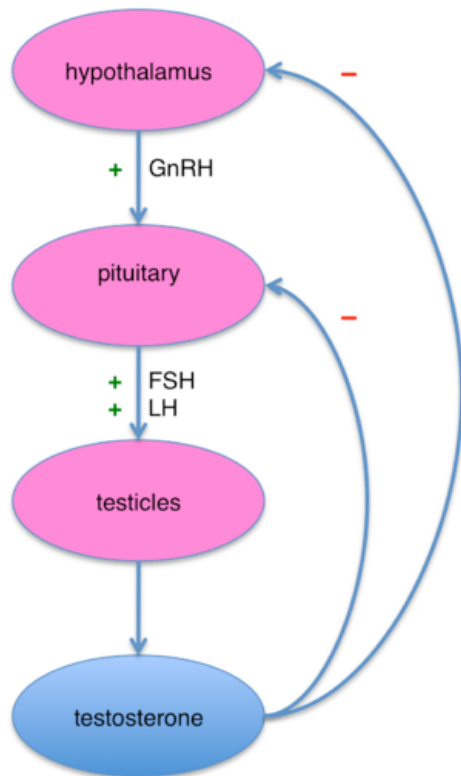


Causes of primary hypogonadism in males

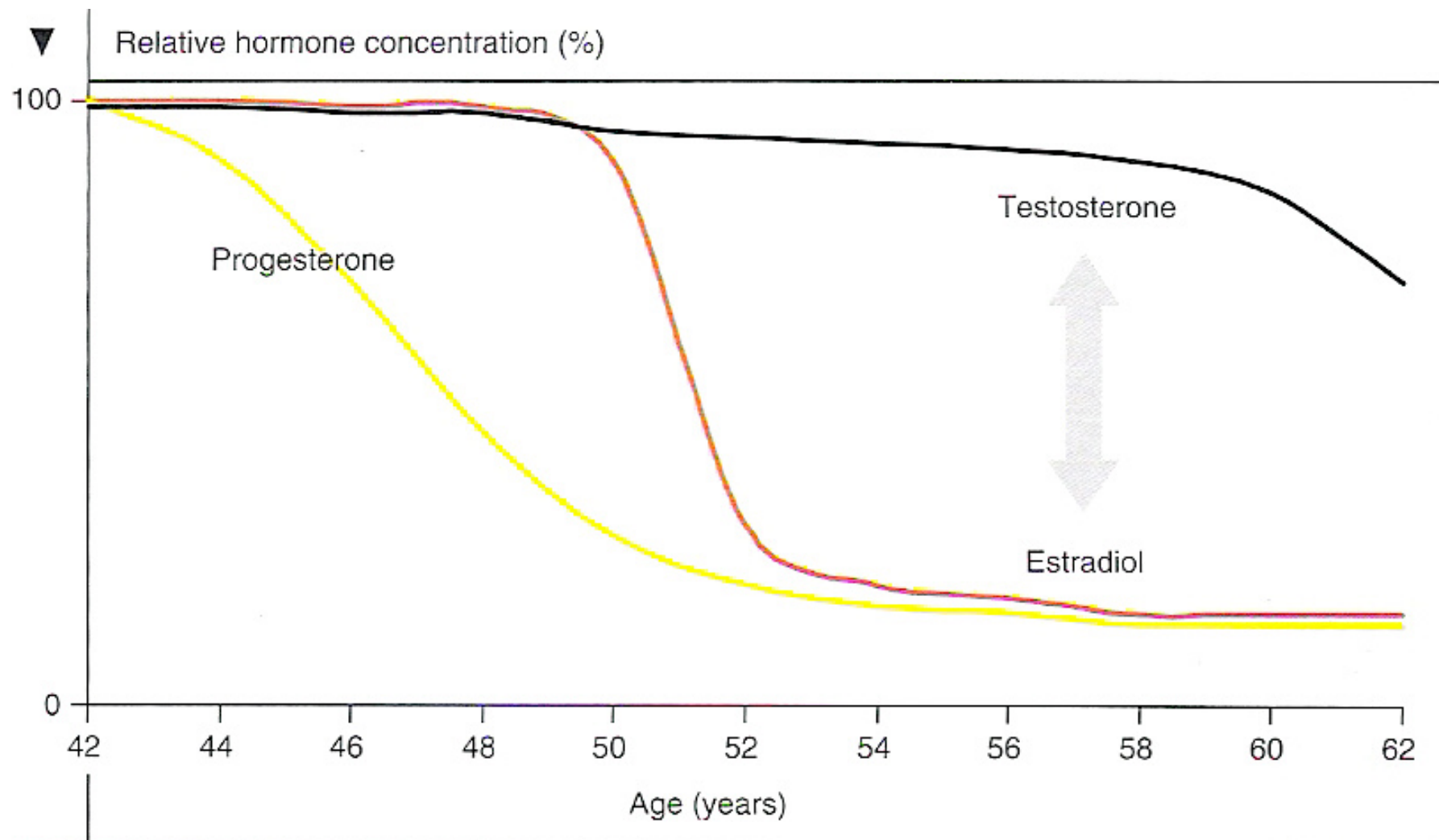
Congenital abnormalities
Klinefelter syndrome
Other chromosomal abnormalities
Mutation in the FSH and LH receptor genes
Cryptorchidism
Varicocele
Disorders of androgen synthesis
Myotonic dystrophy
Acquired diseases
Infections, especially mumps
Radiation
Alkylating agents
Suramin
Ketoconazole
Glucocorticoids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

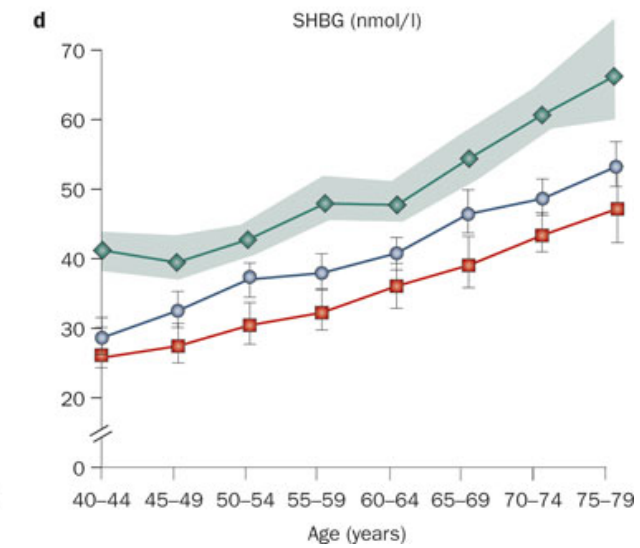
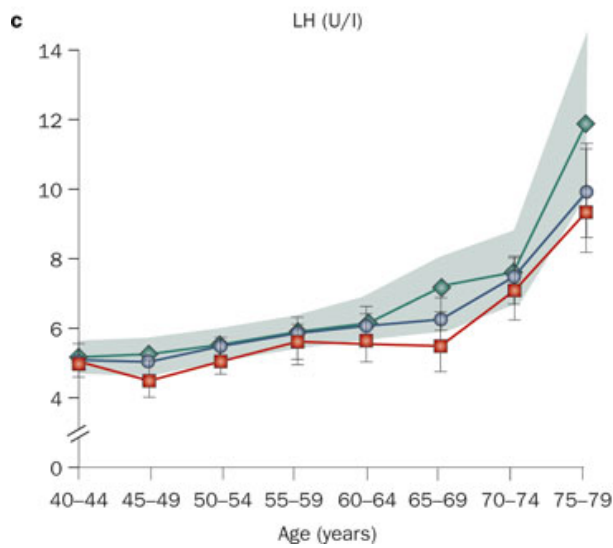
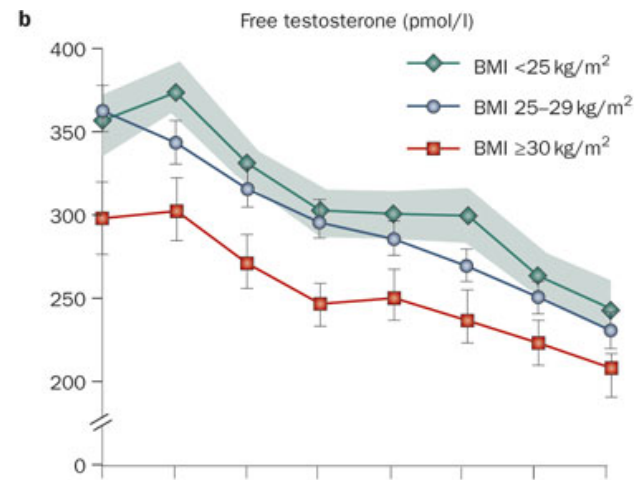
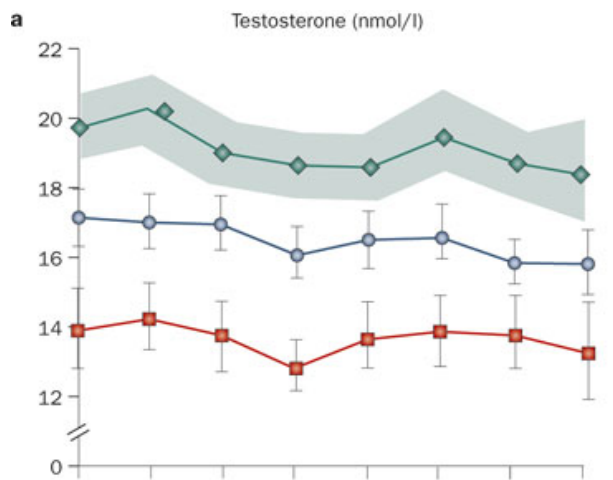
FSH: follicle-stimulating hormone; LH: luteinizing hormone; AIDS: acquired immunodeficiency syndrome.

Late-onset hypogonadism

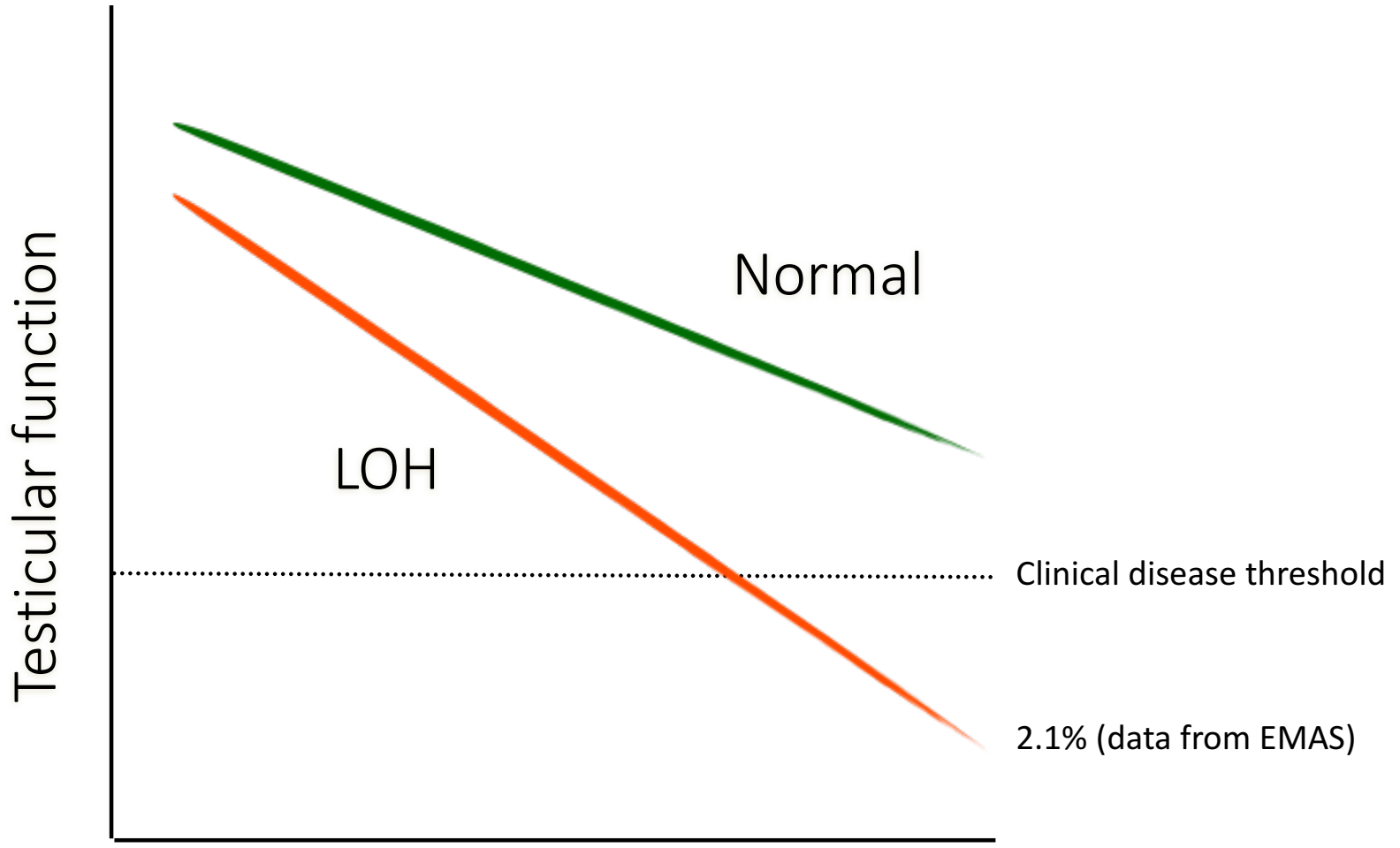


- Failure at both hypothalamus – pituitary and testicular level
- Associated with advanced age
- Clinical picture
- Hormonal profile





LOH



Time

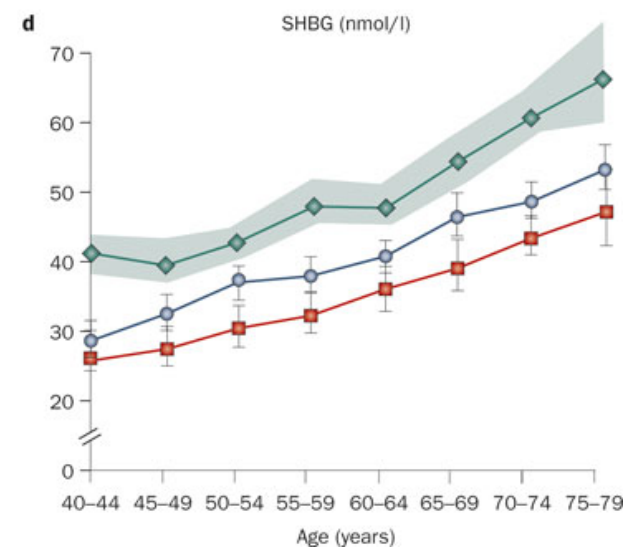
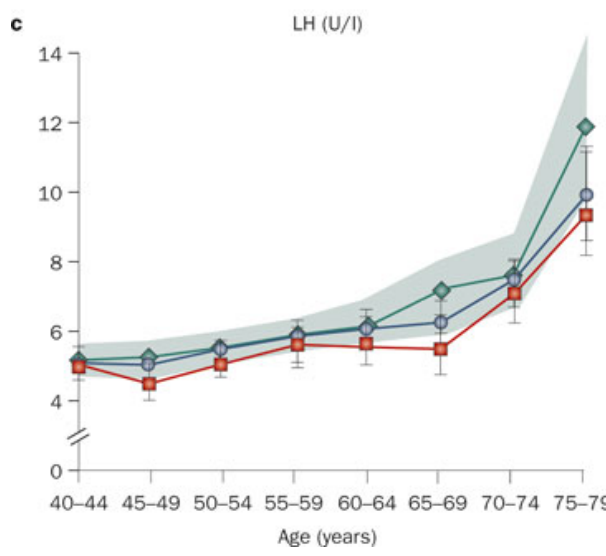
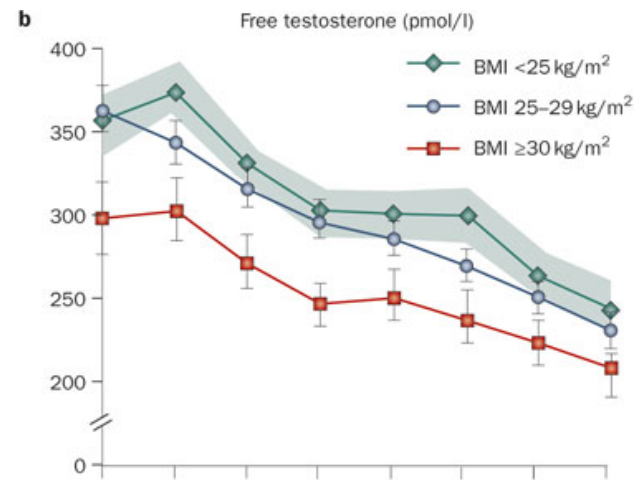
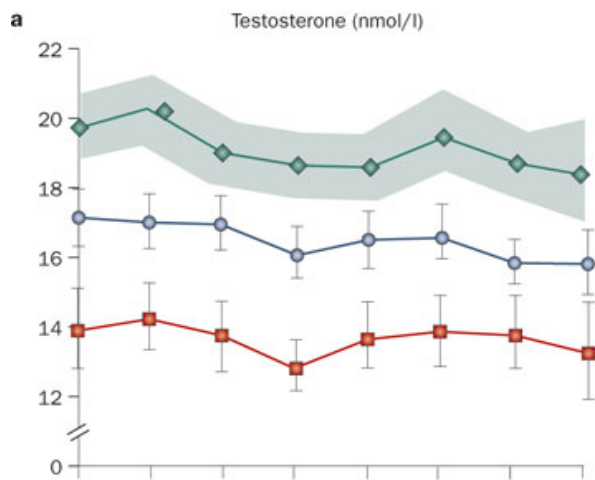
What?

When else do we have to take under consideration?

Metabolic syndrome: definitions

Table 1. Definitions of the metabolic syndrome.					
Organization	WHO	EGIR	AACE	NCEP / ATP III	IDF
Year	1999	1999	2003	2005	2005
Reference no.	(15)	(16)	(17)	(18,19)	(20)
Required	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 ² OR waist > 102 cm (M) OR waist > 88 cm (F)		waist > 94 cm (M) OR > 80 cm (F)*
Additional	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 ²	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.



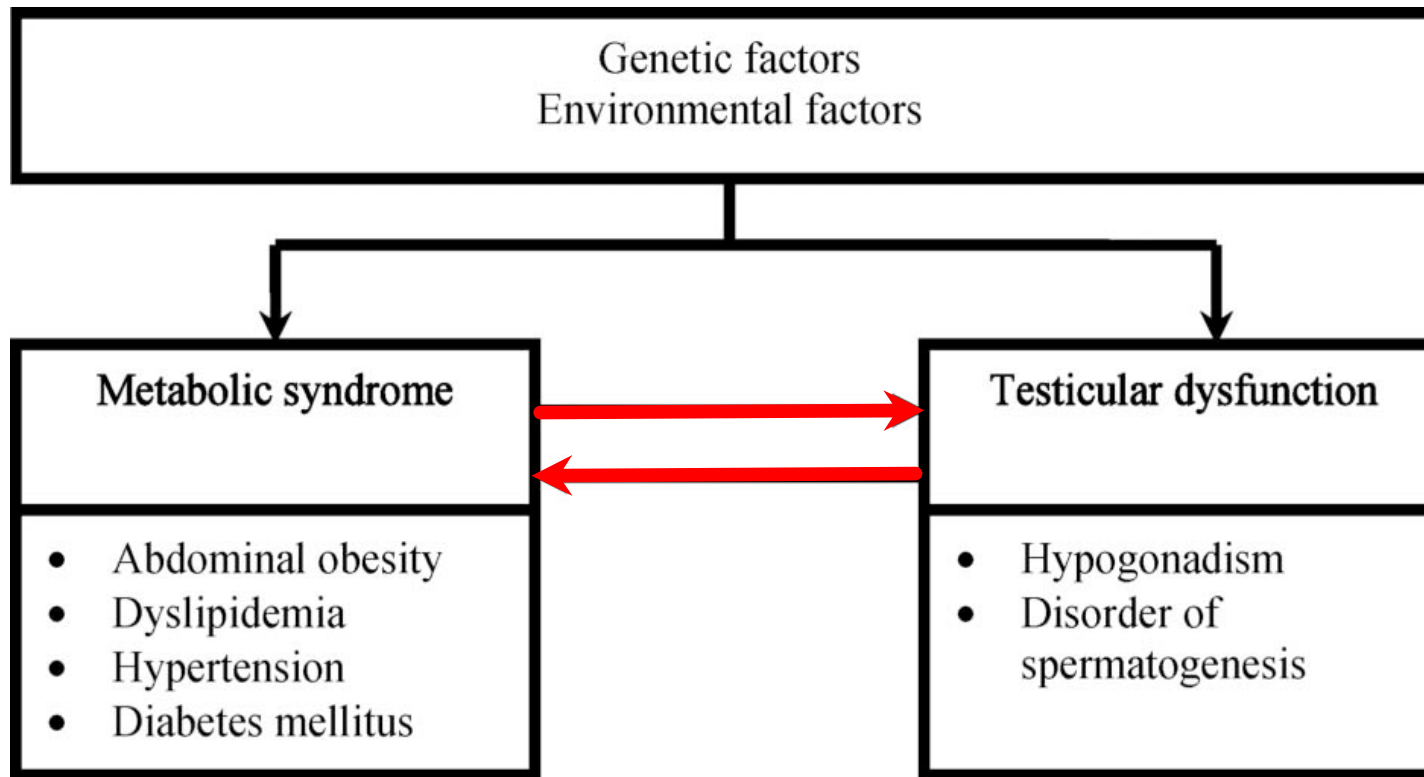
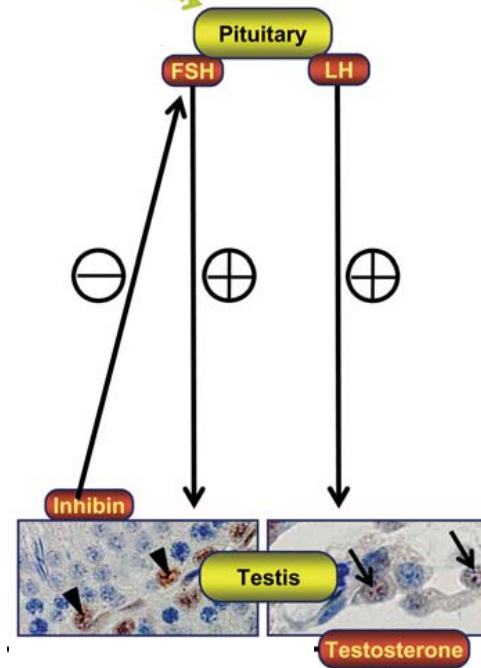
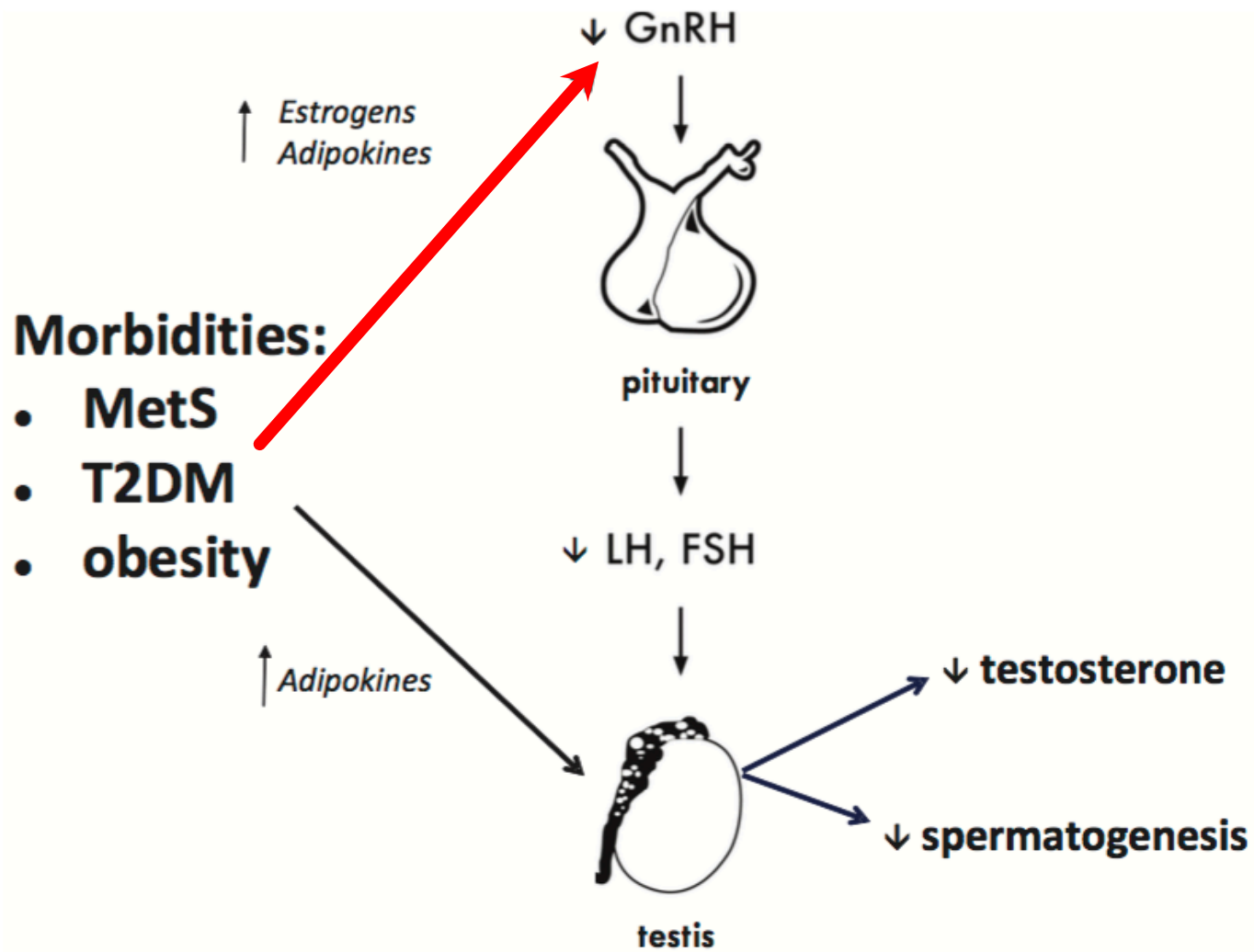
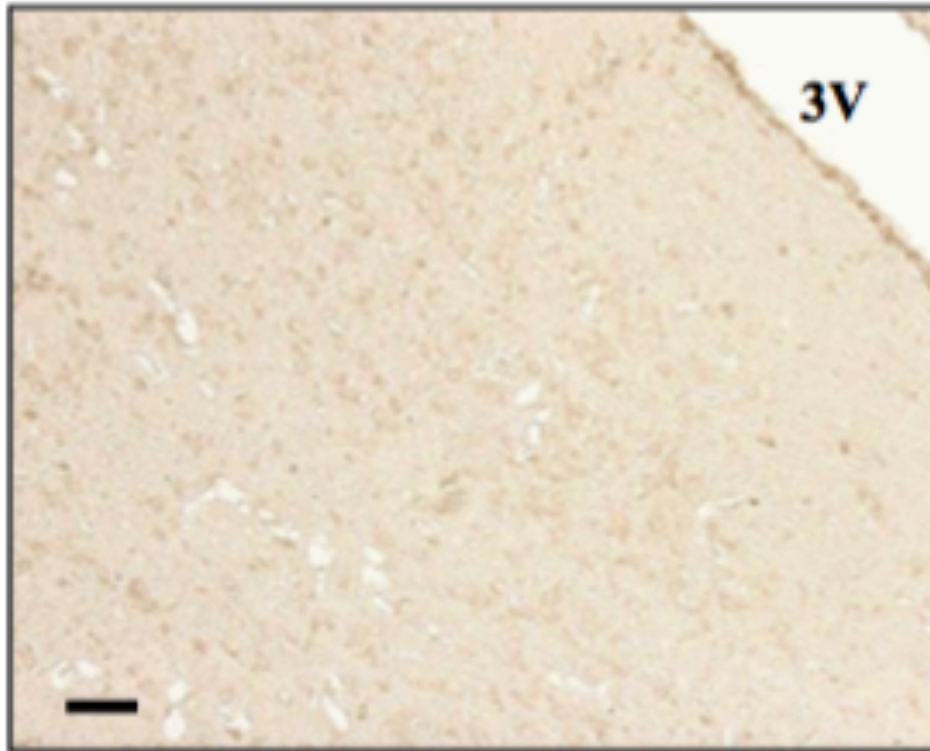


Figure 1. Proposed model of interaction between metabolic syndrome and testicular dysfunction.

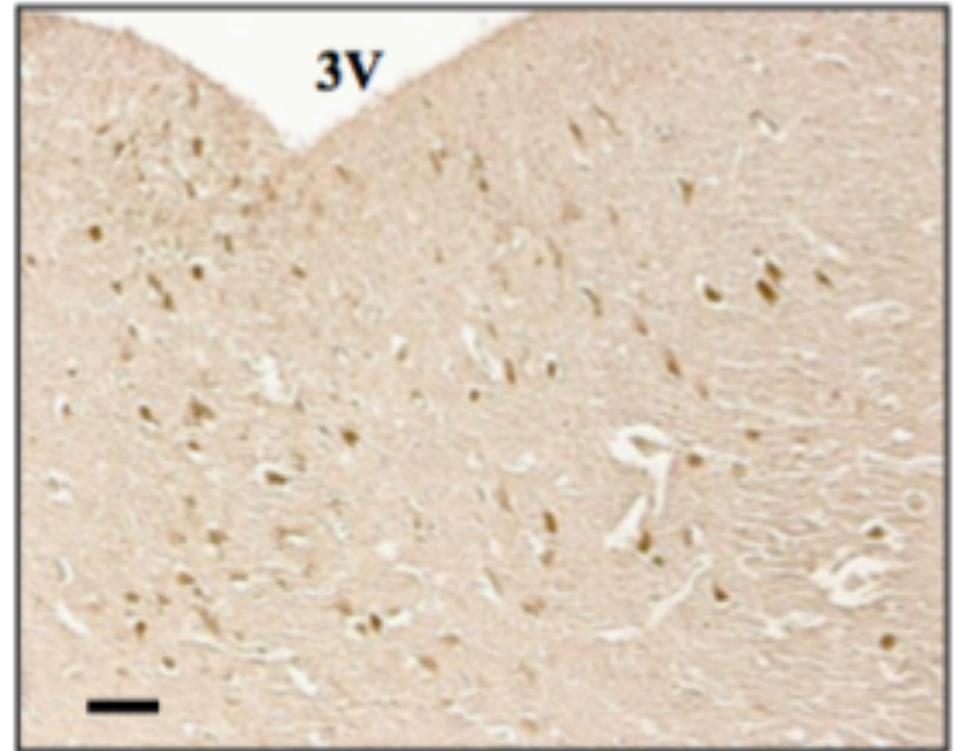




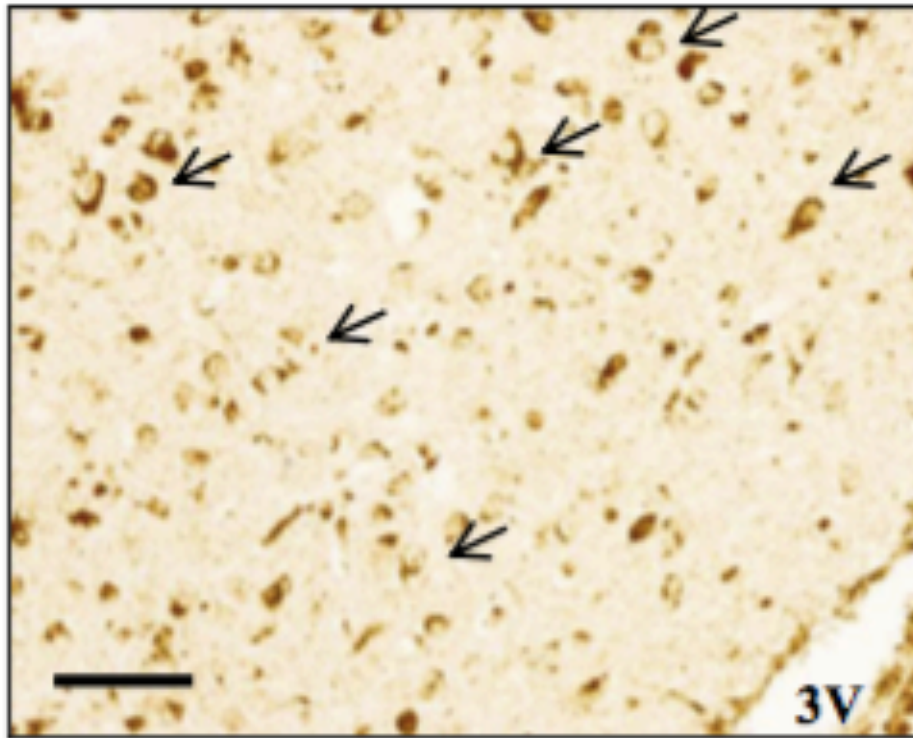
(G) RD, IL-6



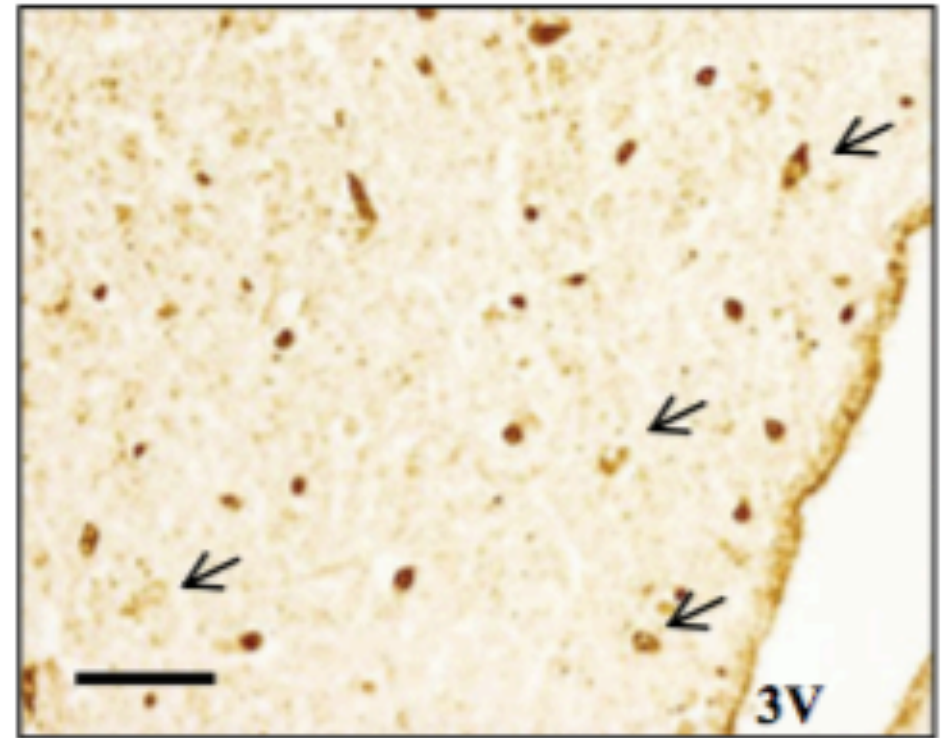
(H) HFD, IL-6



(A) RD, KISS1R



(B) HFD, KISS1R

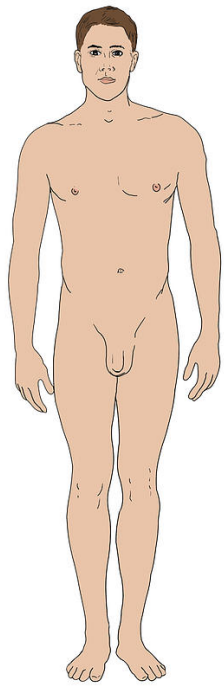




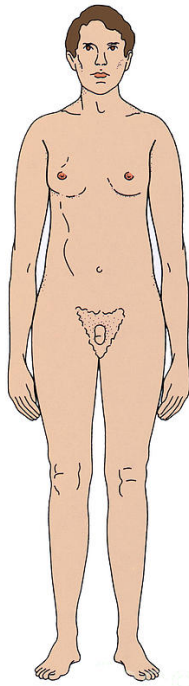
When?

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

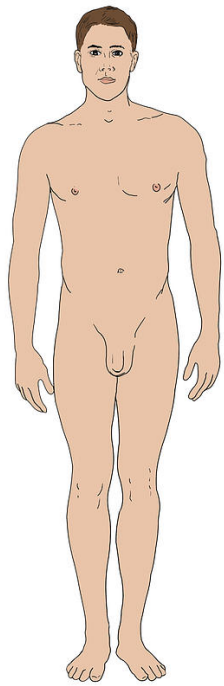
Gene	OMIM	CTO	CHH phenotypes			Overlapping syndromes										
			KS	CHH	CHH reversal	CPHD	CPHD + SOD	WS	CHARGE	HS	SHFM	D-WS	MGS	PEPNS	GHS	
<i>KAL1 (ANOS1)</i>	300836	✓	✓	×	✓	×	×	×	×	×	×	×	×	×	×	×
<i>SEMA3A</i>	614897	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×
<i>SOX10</i>	602229	×	✓	×	×	×	×	✓	×	×	×	×	×	×	×	×
<i>OL14RD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

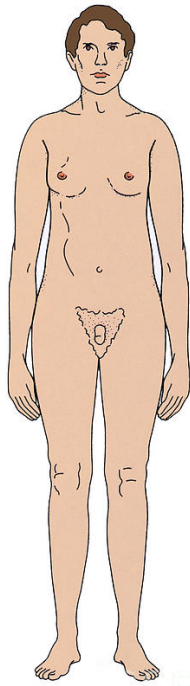
Clinical spectrum of Kallmann's syndrome

- 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

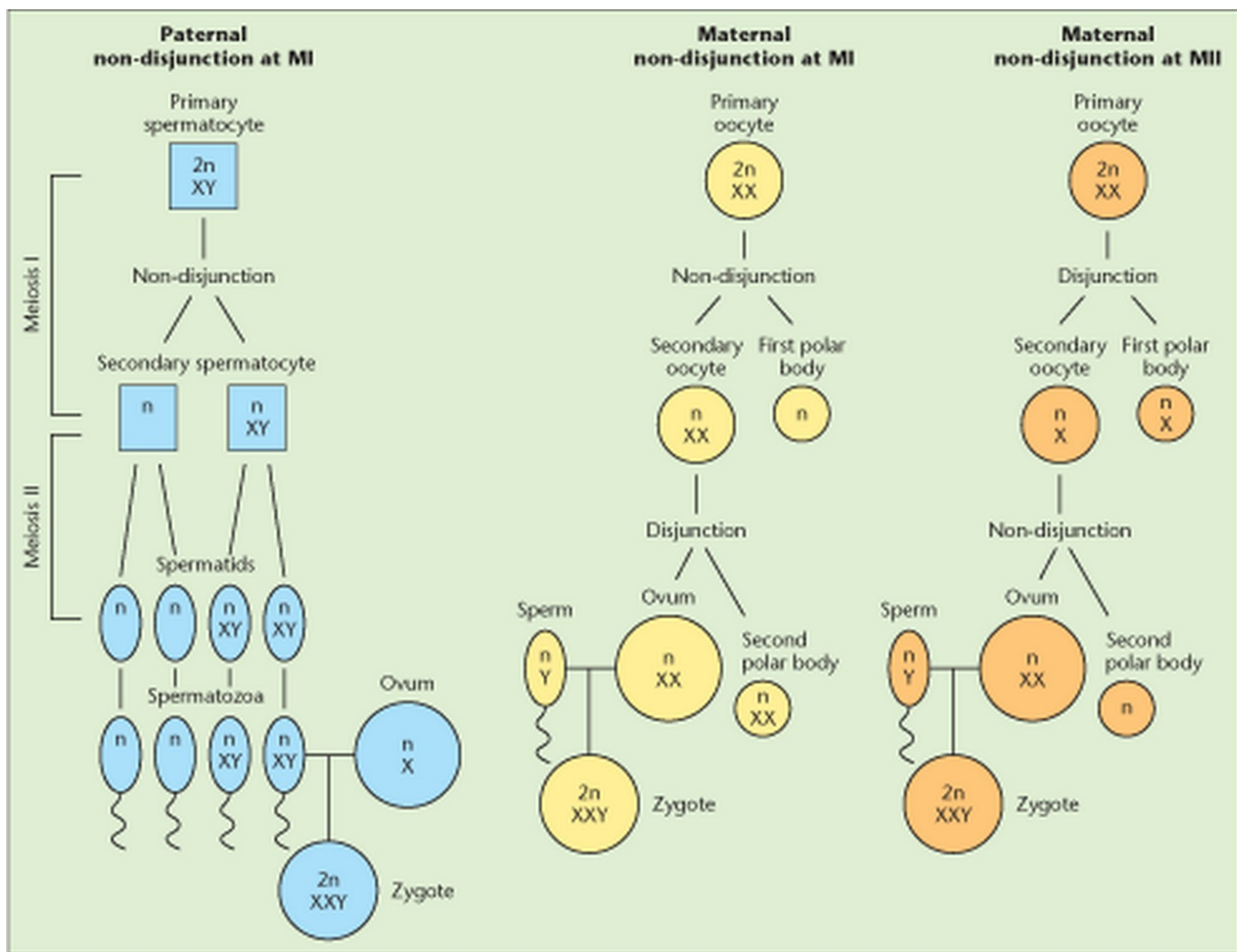
- Always
- Treat hypogonadism
- Treat co-morbidities
- Treat infertility

Co-morbidities

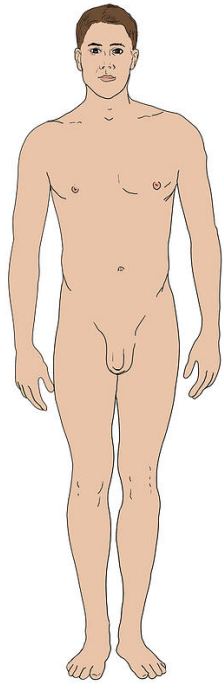
Comorbidities in Klinefelter syndrome: prevalence and mortality

	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

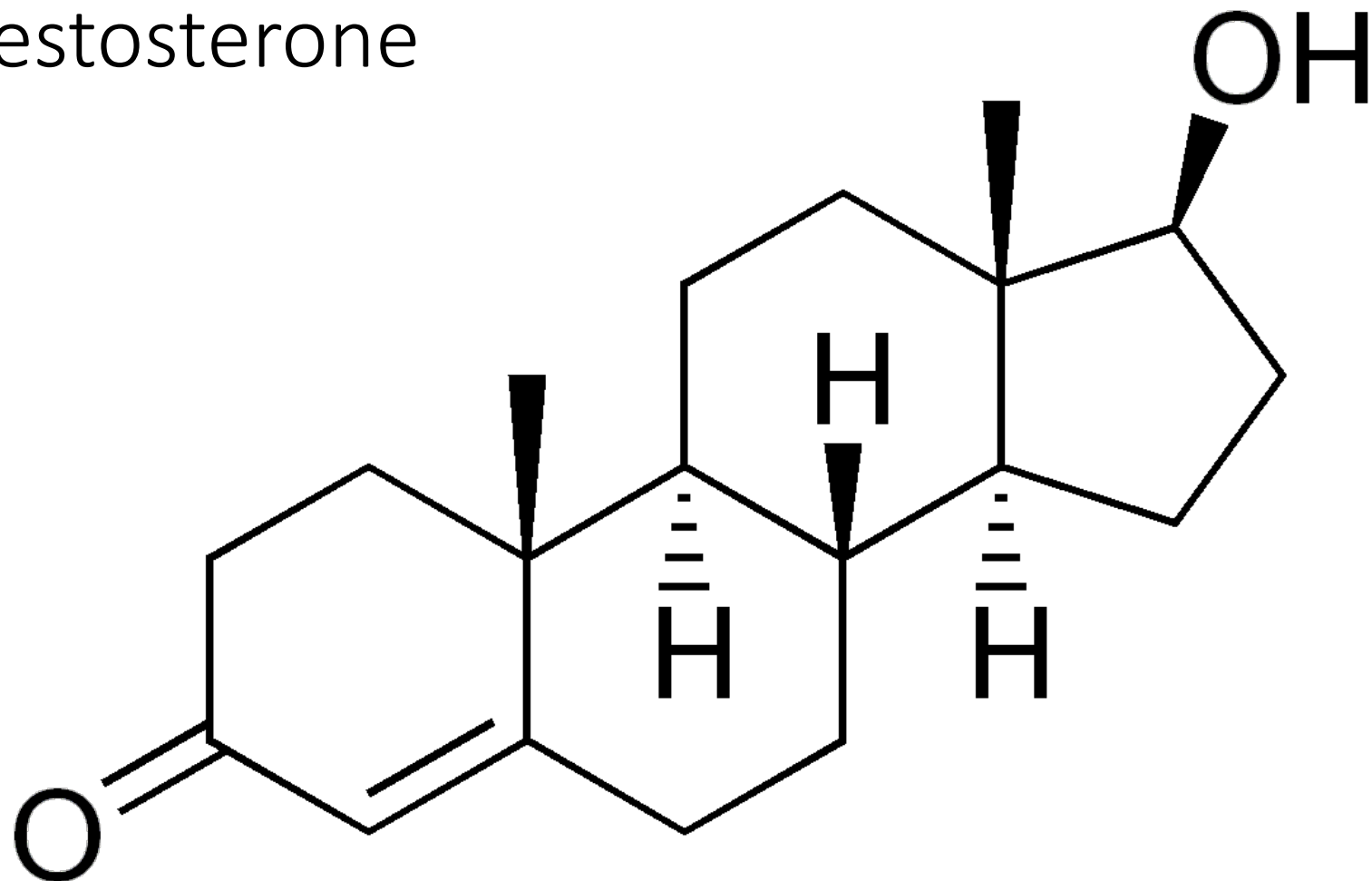
Table 2. Identification and Prevalence of Symptoms Related to Testosterone in the Training Set.*

Question Regarding Symptom	Evaluation Tool	Symptomatic Men	Asymptomatic Men	Symptom Prevalence	P Value	
					Total Testosterone	Free Testosterone
Sexual symptoms				%		
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
Physical symptoms						
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
Psychological symptom						
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

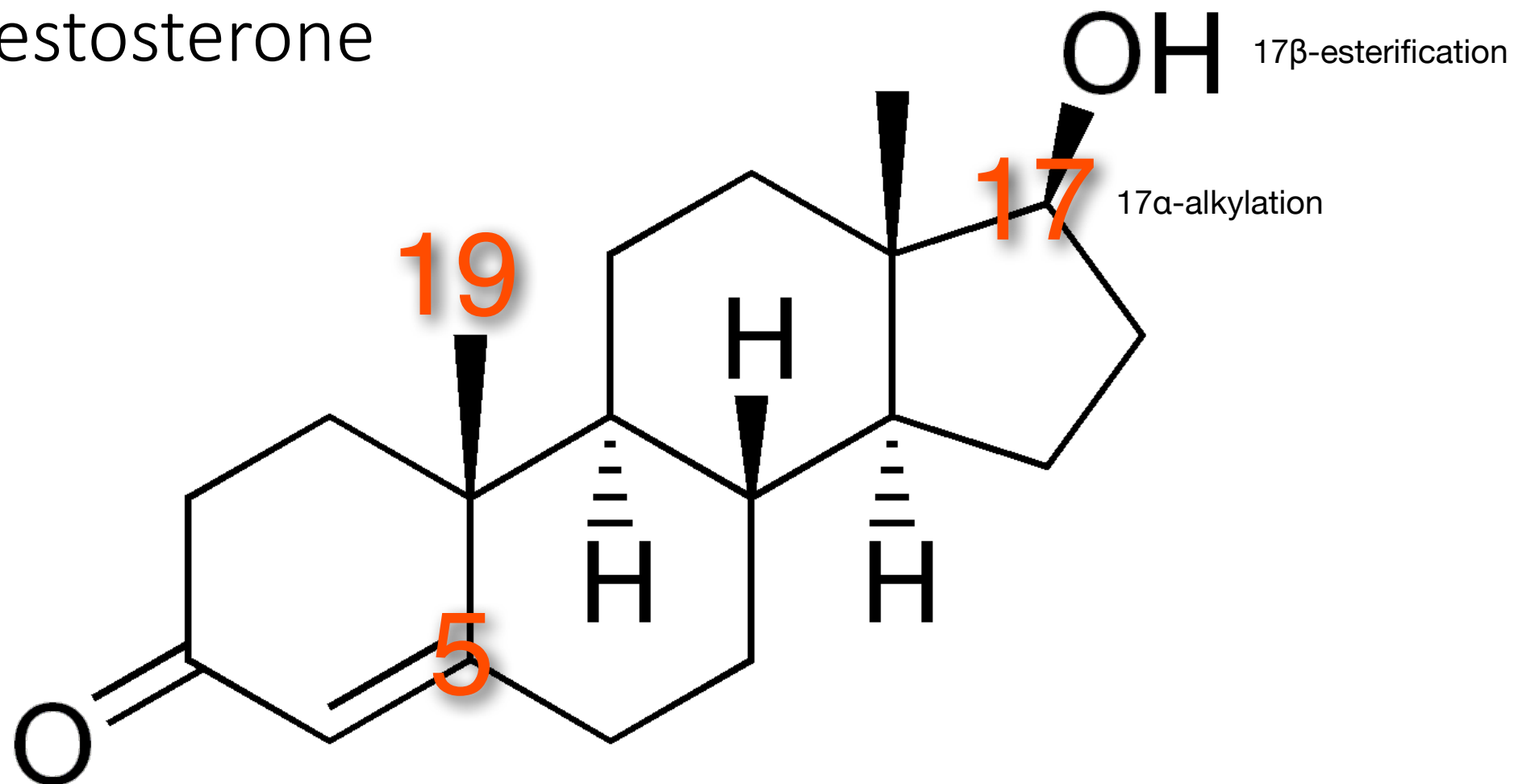
How?

How do we treat hypogonadism?

Testosterone

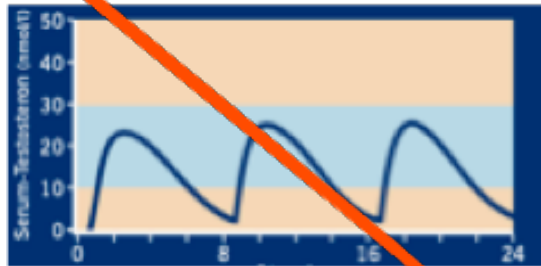


Testosterone



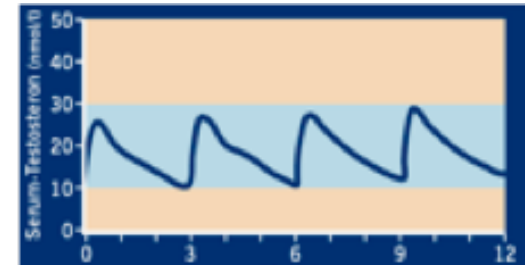
Testosterone replacement therapy

Per os:
3-4 tabs
per day



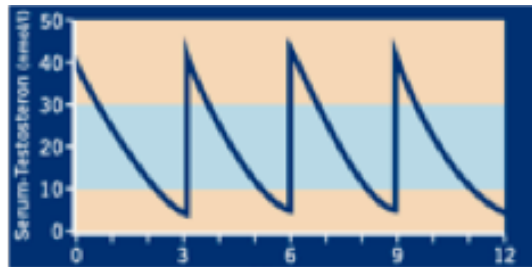
Hours

IM:
every 10-14
weeks



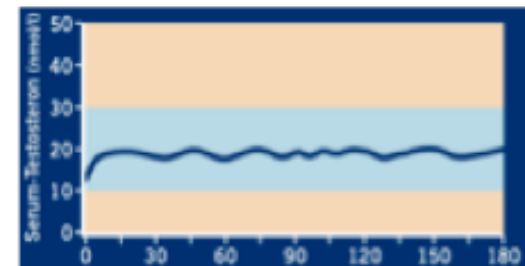
Months

IM:
every 2-3
weeks



Weeks

Gel:
every day

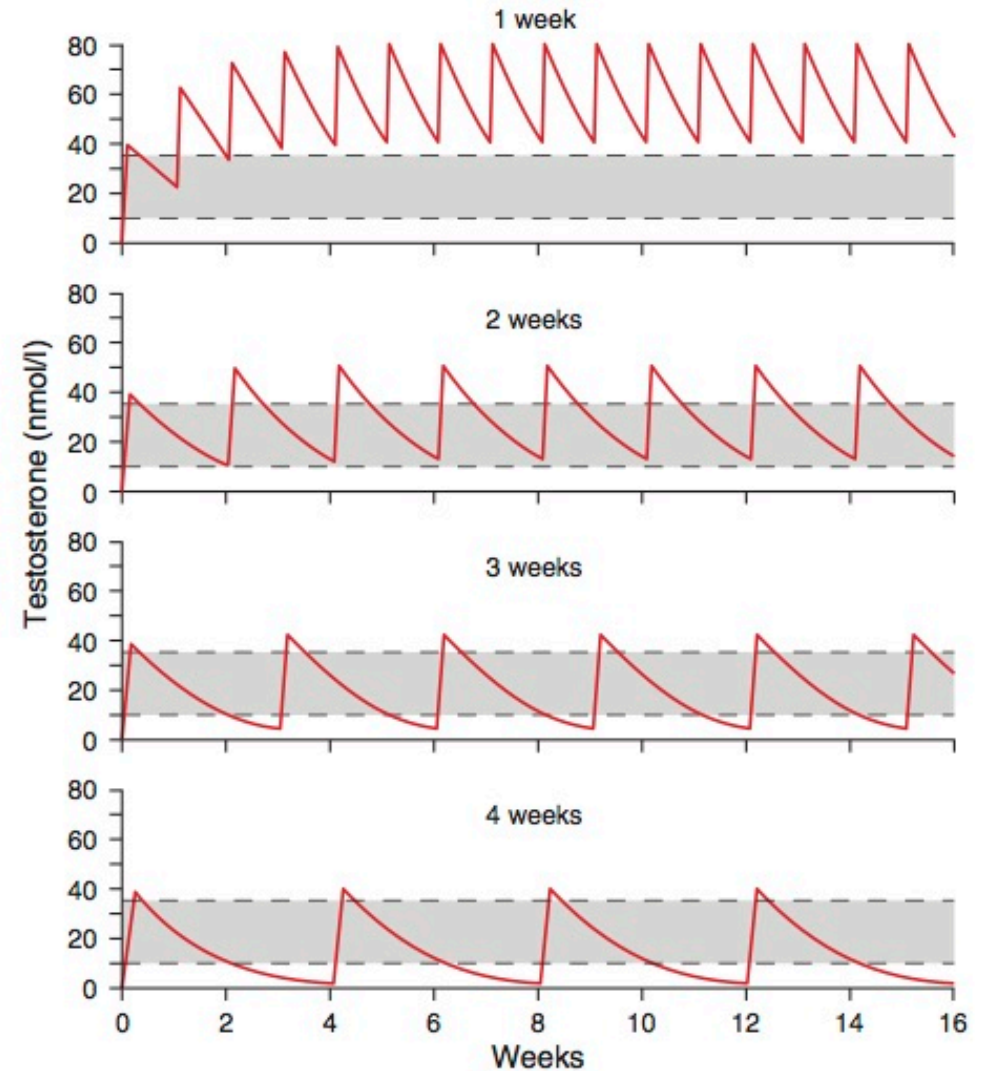










Hours

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

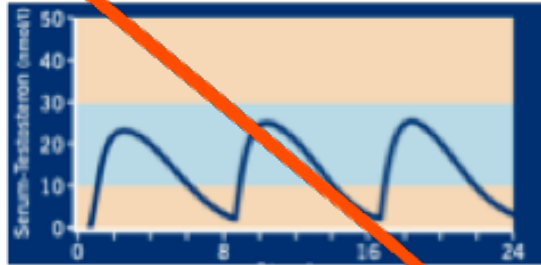
Laboratory parameters

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



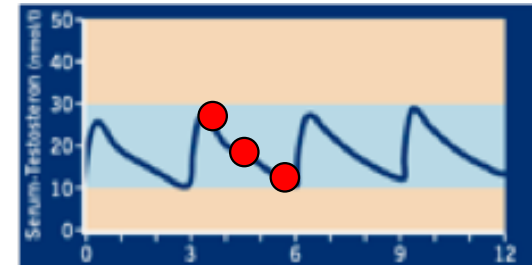
Testosterone replacement therapy

Per os:
3-4 tabs
per day



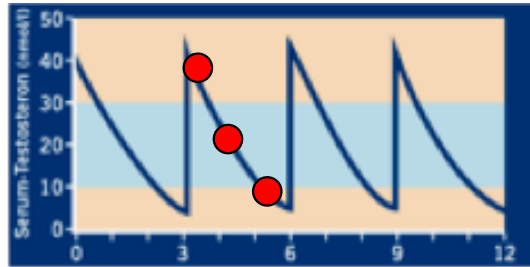
Hours

IM:
every 10-14
weeks



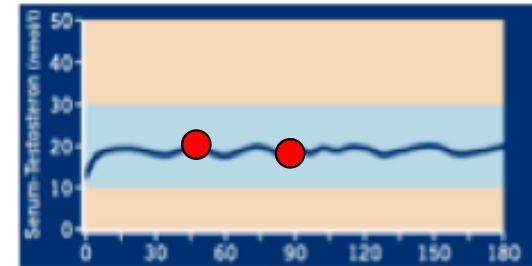
Months

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Weeks

Gel:
every day



Hours

Patch:
every day

The NEW ENGLAND
JOURNAL *of* MEDICINE

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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 ≥ 1.0 ng/ml	8	23
Prostate cancer	0	1
IPSS >19 [†]	26	27
Hemoglobin ≥ 17.5 g/dl	0	7
Cardiovascular event [‡]		
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 [§]	6	7

What?

What else can we do to treat hypogonadism?

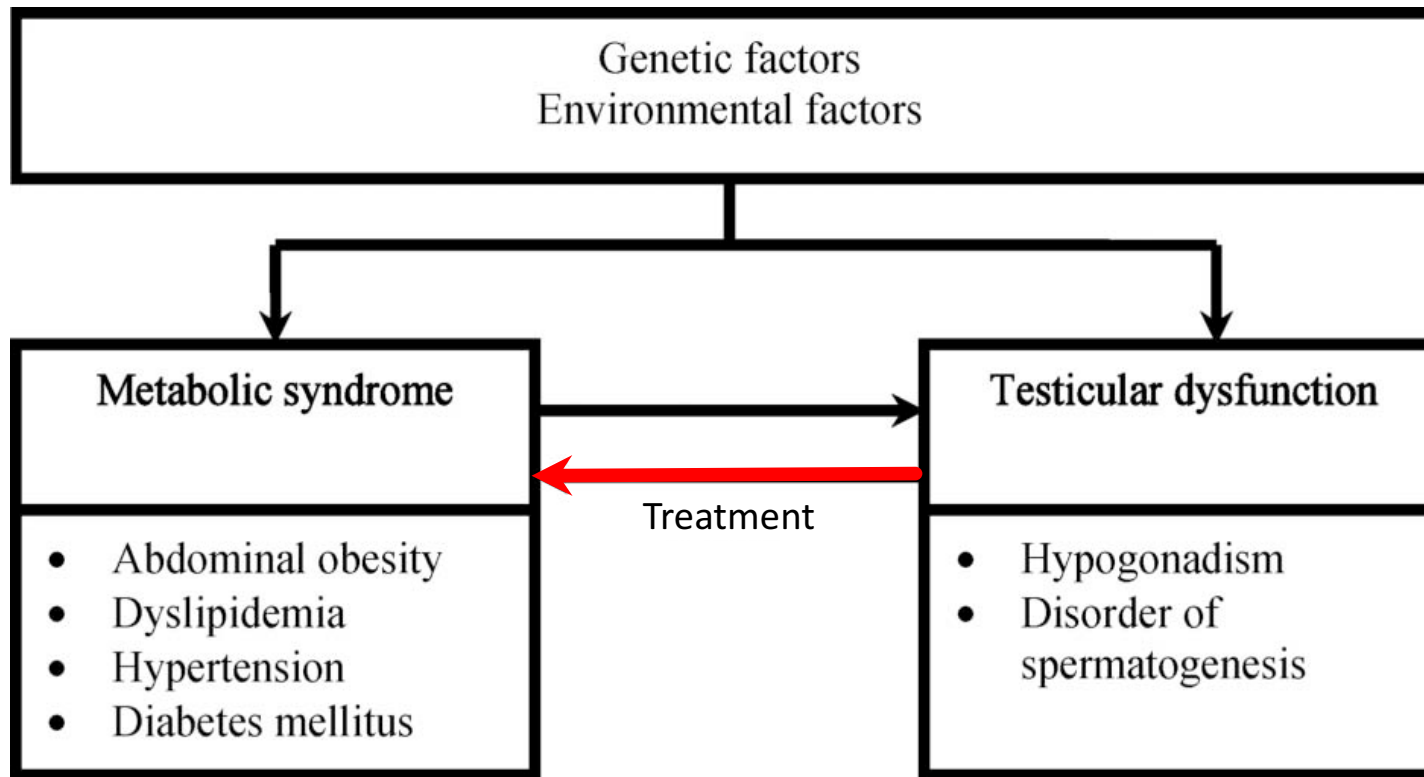
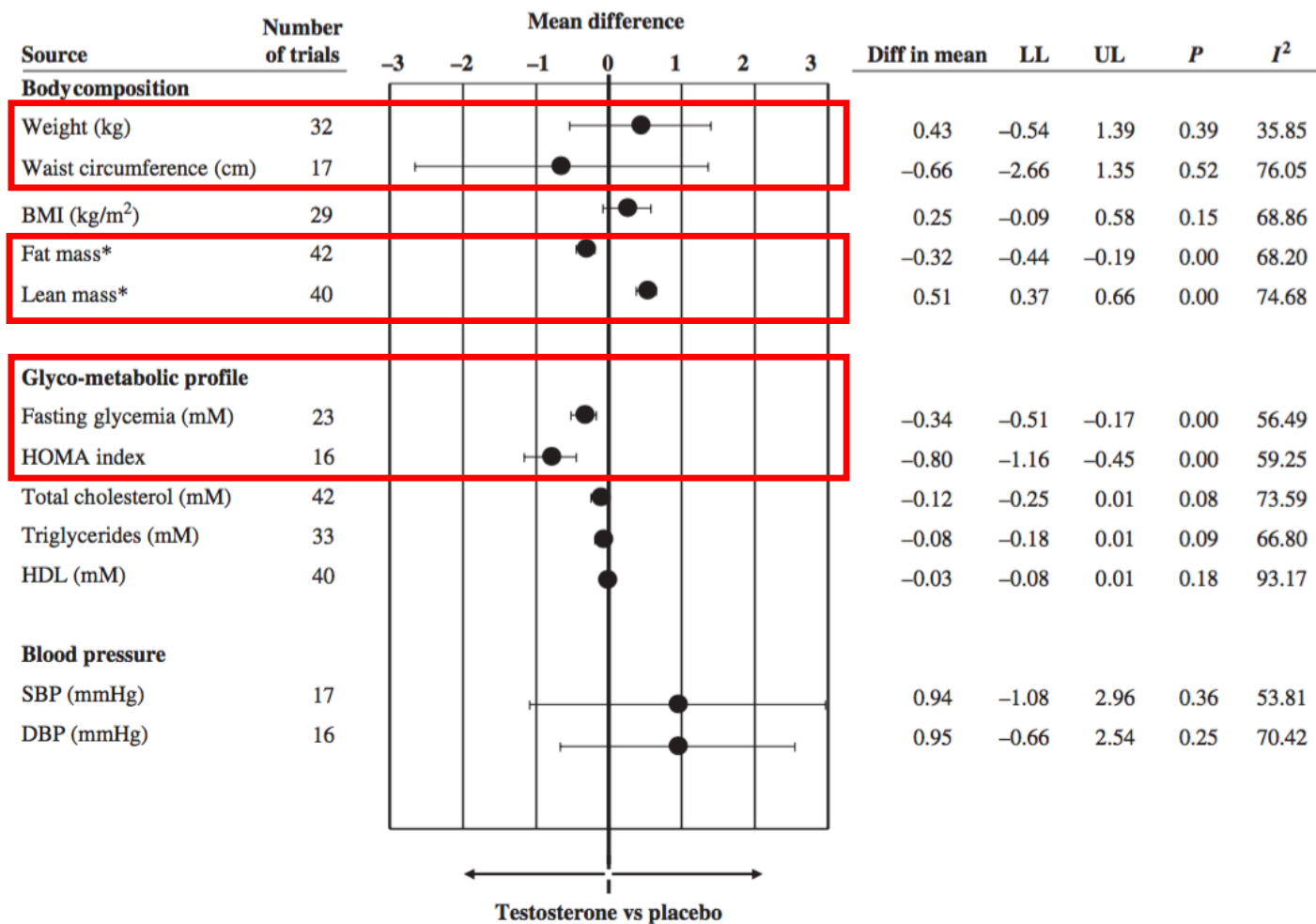


Figure 1. Proposed model of interaction between metabolic syndrome and testicular dysfunction.



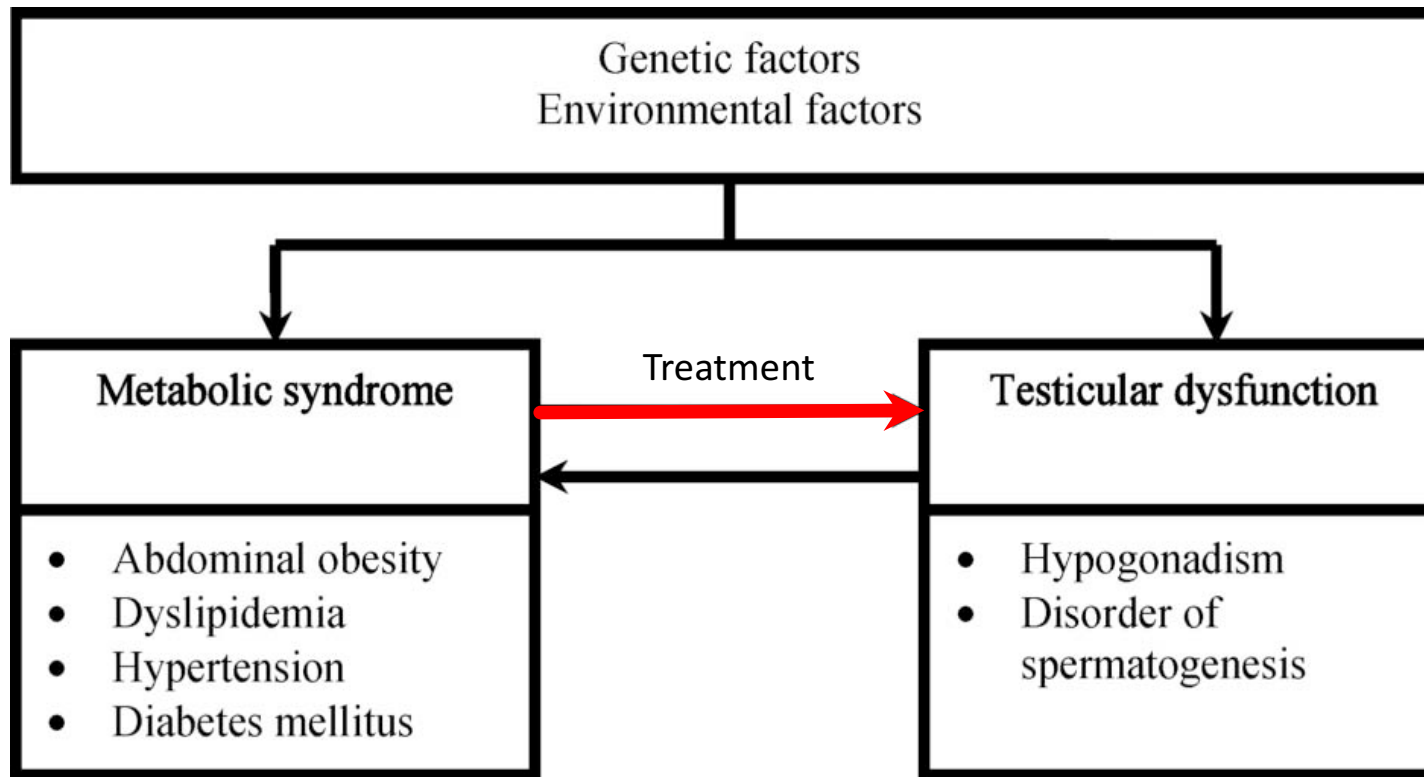
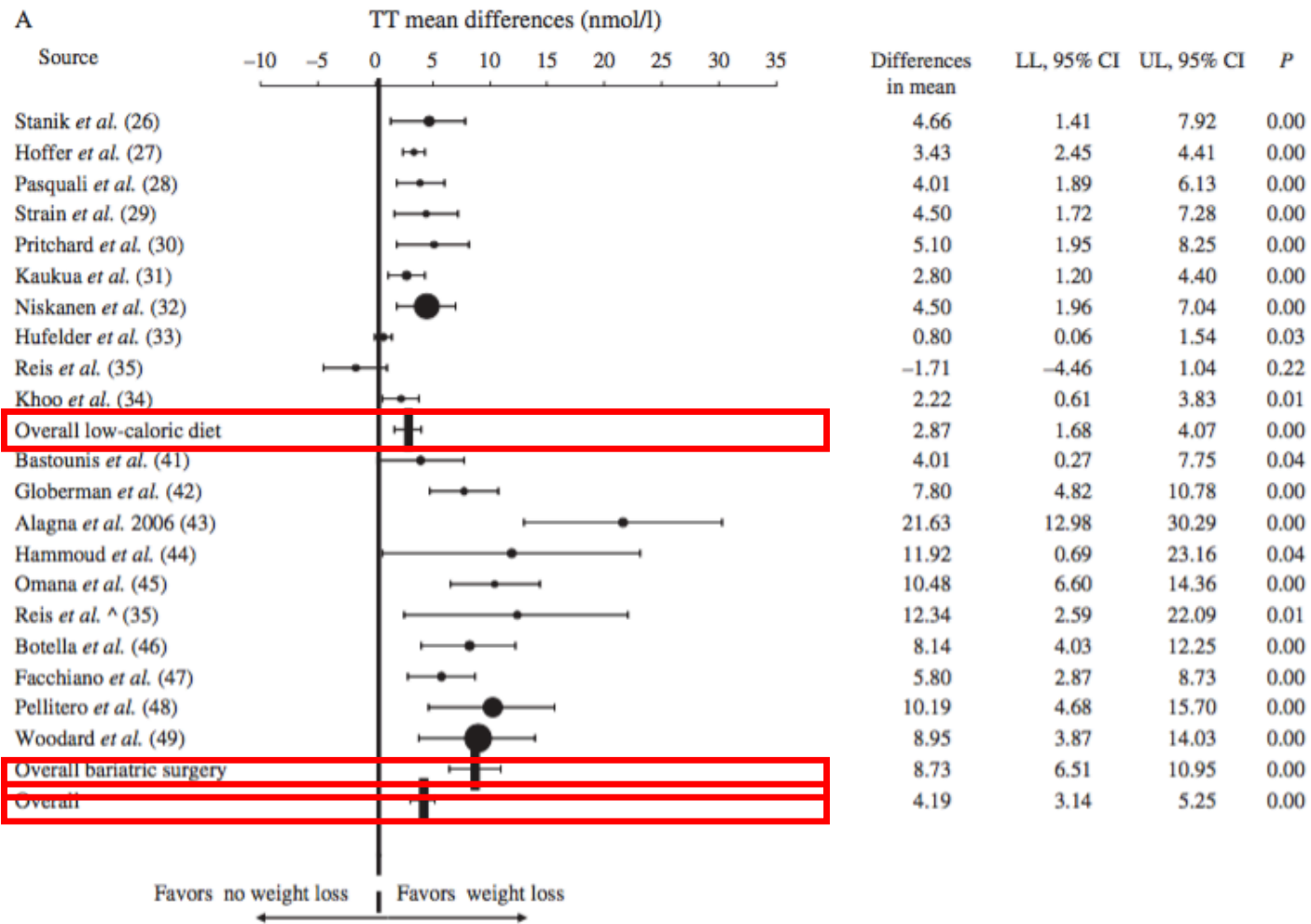
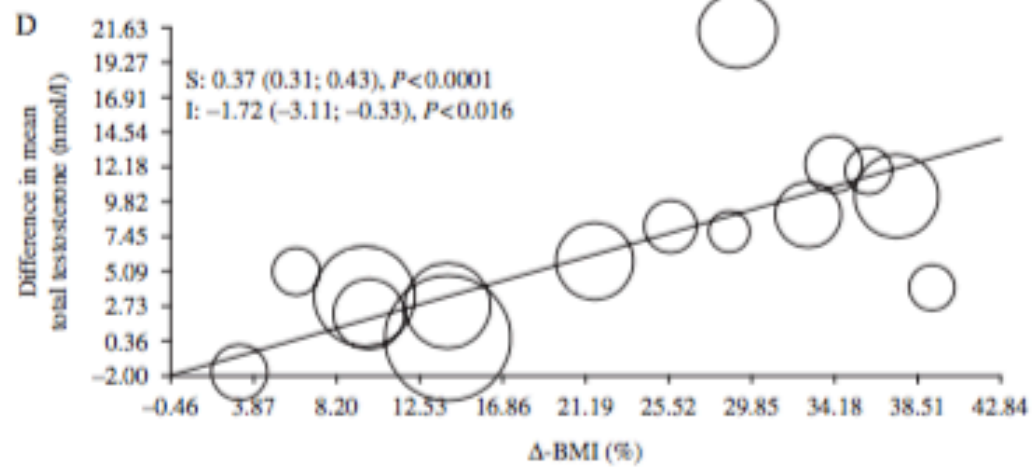
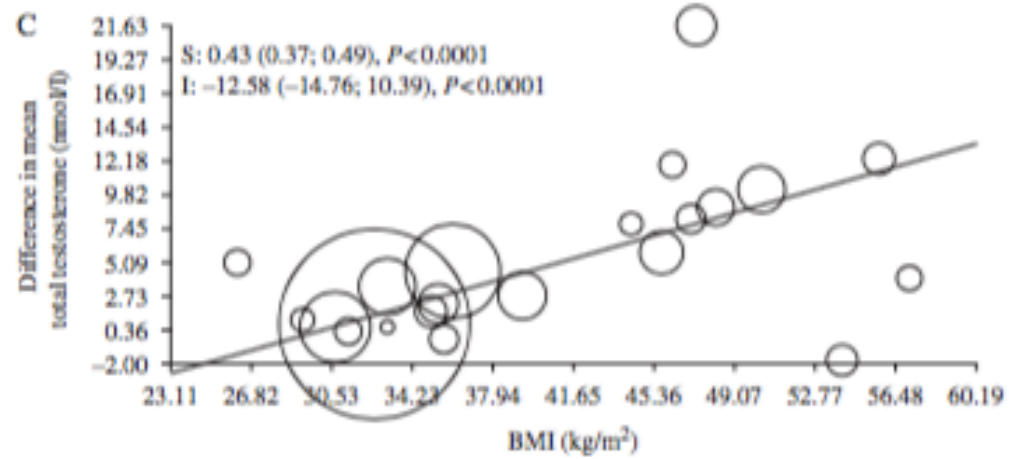


Figure 1. Proposed model of interaction between metabolic syndrome and testicular dysfunction.





How?

How do we summarize?

What we will do

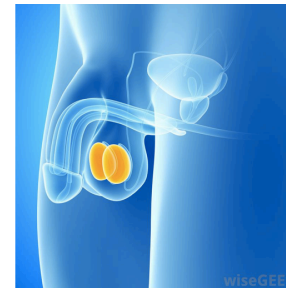
- Provide current concepts of male hypogonadism
- Discuss practical issues of testosterone supplementation
- Emerge the role of life-style interventions on the management of male hypogonadism

Hypogonadism

- Definition

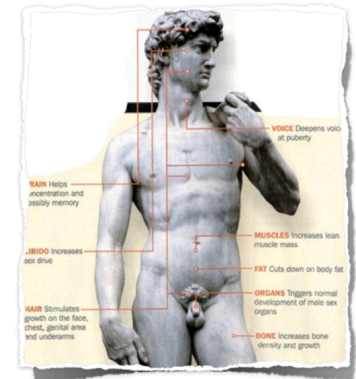
- Clinical picture

Testicular function



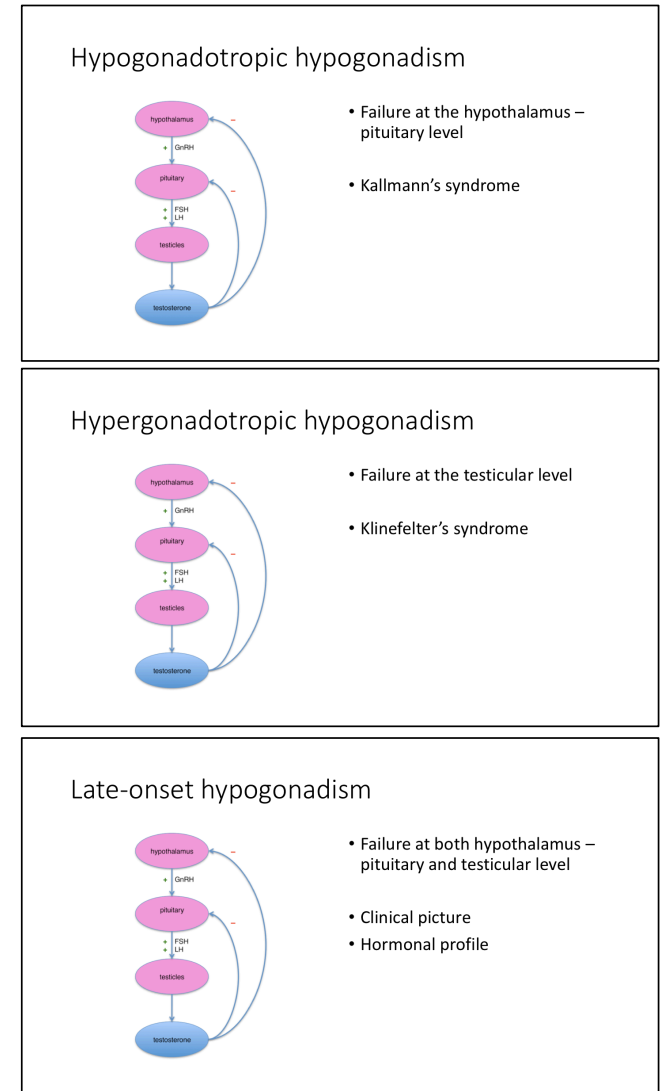
- Failure of endocrine function
 - Low serum testosterone
 - Male hypogonadism
- Failure of exocrine function
 - Poor sperm quality
 - Male infertility

Testosterone actions



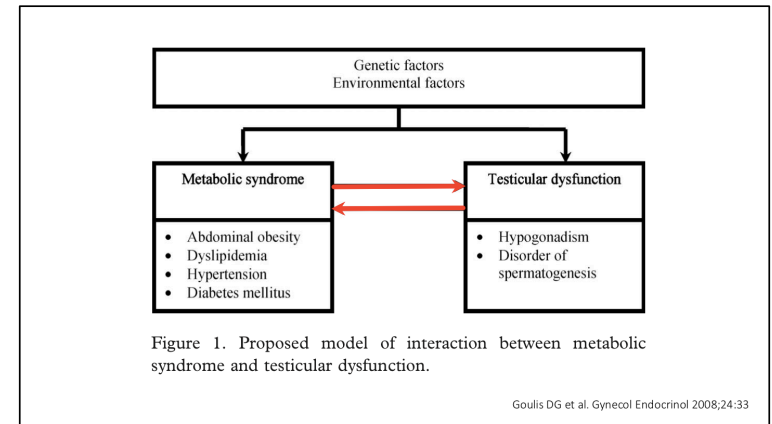
Types of hypogonadism

- Hypogonadotropic hypogonadism
- Hypergonadotropic hypogonadism
- Late-onset hypogonadism



Pathophysiology

- Connection of hypogonadism to obesity



T replacement therapy

- Contra-indications

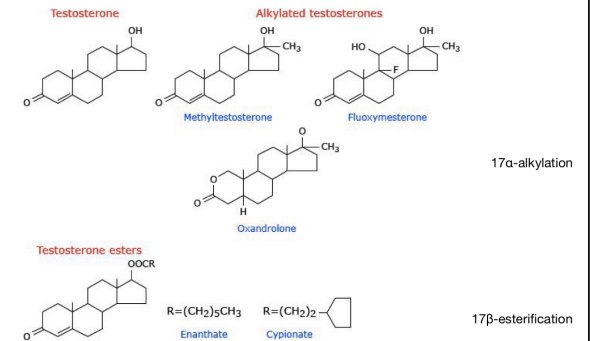
- Preparations

- Routes of administration

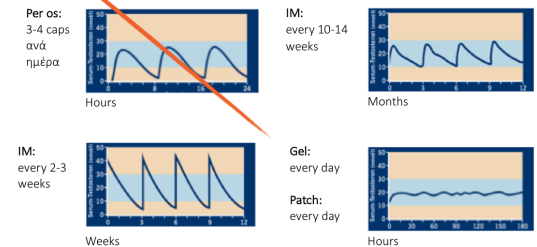
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- Heart failure (uncontrolled)
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Testosterone replacement therapy



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
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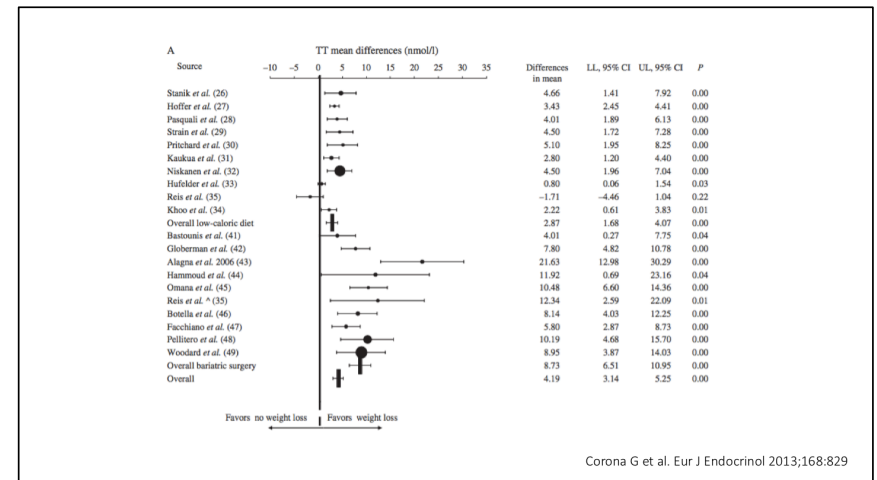
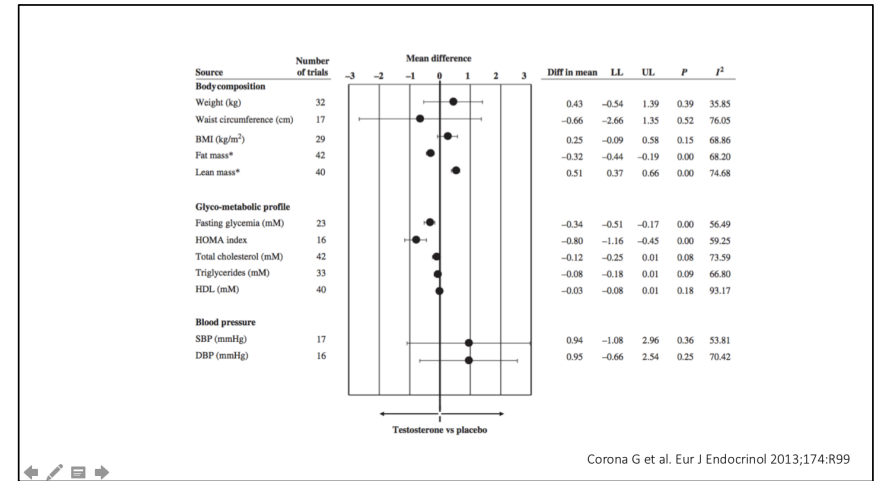
Under investigation

- 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?

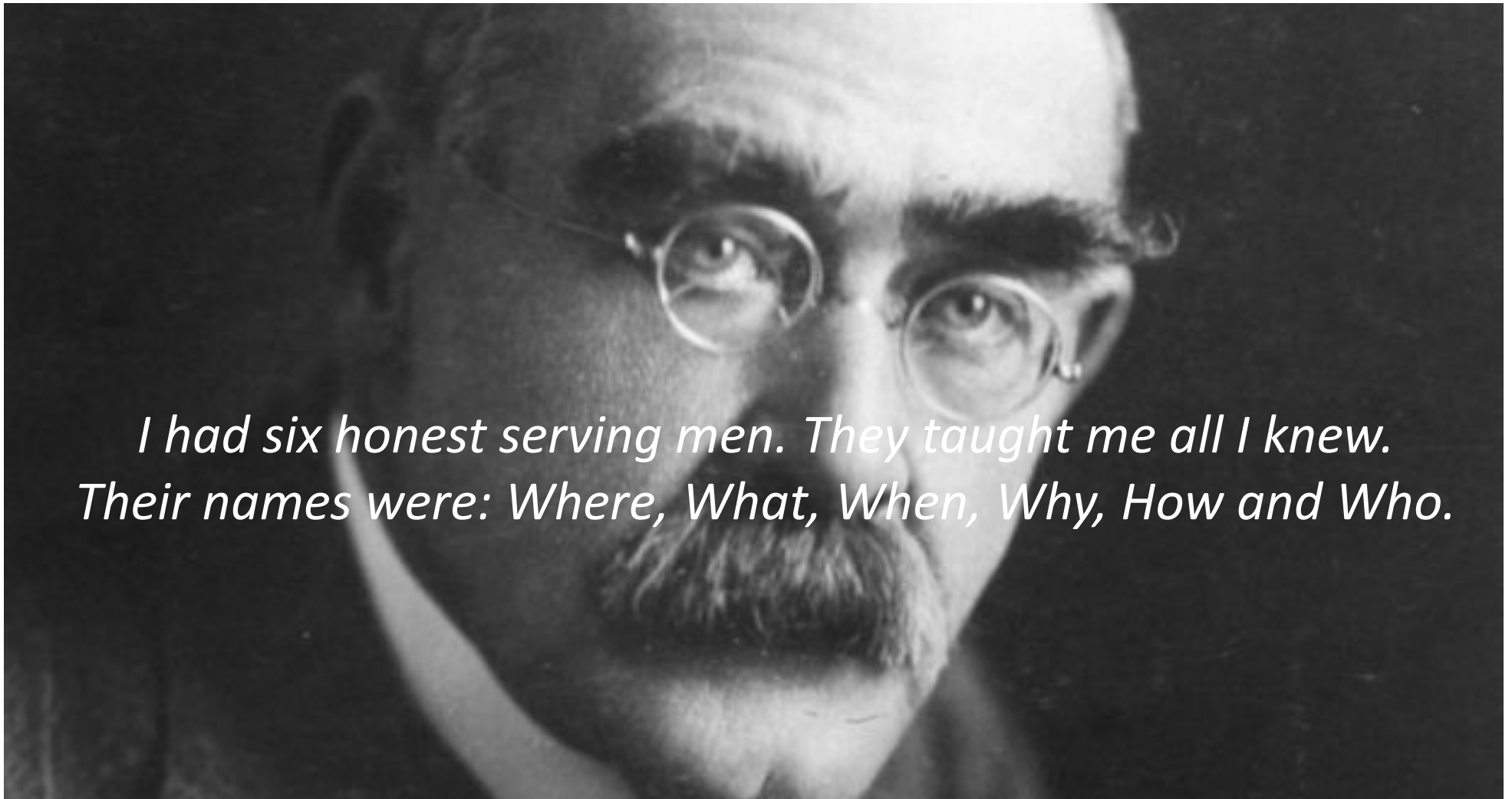
How do we conclude?

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)

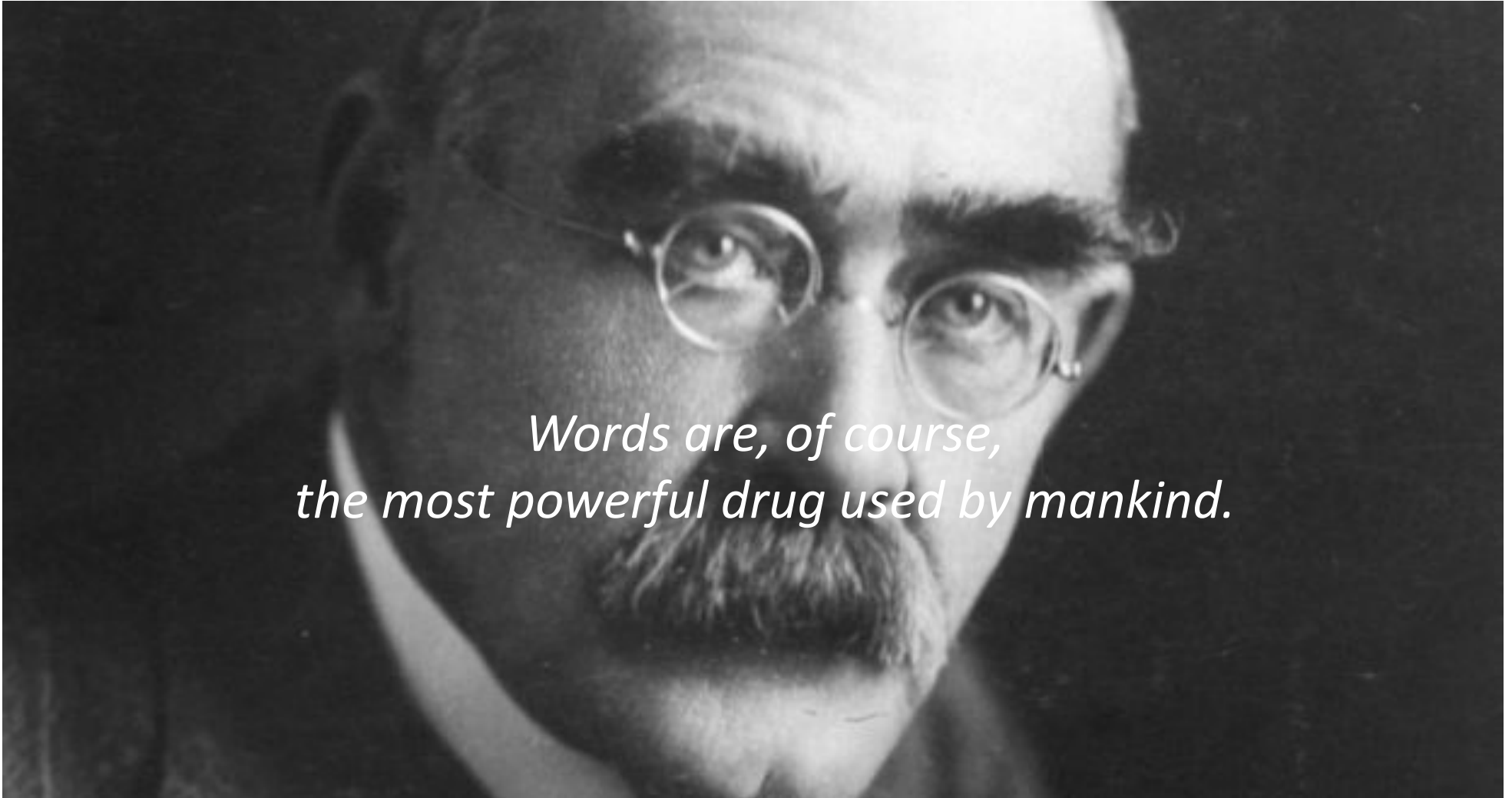
What don't we know?

- 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 spectacles and has a prominent mustache. The lighting is dramatic, with strong highlights on his forehead and the bridge of his nose, and deep shadows on the sides of his face. The background is dark and indistinct.

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

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.

*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
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A.-G. Kouthouris (urologist)
I. Koutsogiannis (urologist)
K. Toulis (endocrinologist)
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N. Athanasiadi (dietician)
V. Harizopoulou (midwife)
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