University of Perugia
Department of Medicine & Surgery
Direttore "Centro Biotecnologico Internazionale di Ricerca Traslazionale ad Indirizzo Endocrino, Metabolico ed Embrio riproduttivo (CIRTEMER)"

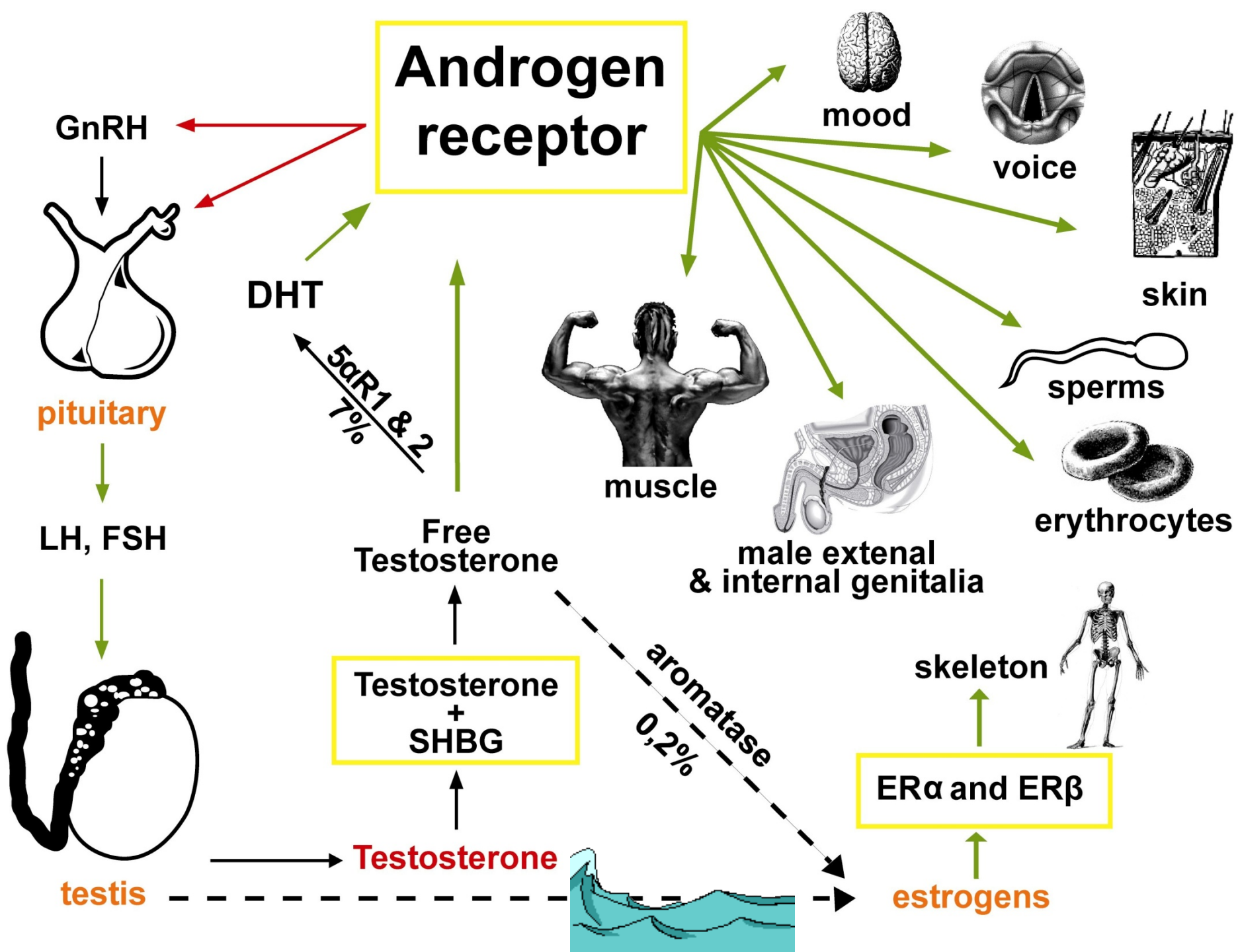
Azienda Ospedaliera "S. Maria" di Terni
SSVD di Andrologia Medica ed Endocrinologia della Riproduzione
(Responsabile f.f.: Prof. Giovanni LUCA)

GIOVANNI LUCA (MD. PhD)

Professore Associato (Med/50), Università degli Studi di Perugia
Collaborative Associate Professor, Department of Internal Medicine, University of South Florida, Tampa, USA
Responsabile S.S.D. di Andrologia Medica ed Endocrinologia della Riproduzione, Azienda Ospedaliera "S. Maria" di Terni
Referente SC di Diabetologia, Dietologia e Nutrizione Clinica., Azienda Ospedaliera "S. Maria" di Terni

Ipogonadismo late-onset: una malattia metabolica?

CENT'ANNI DI DIABETOLOGIA: UNA SCIENZA IN CONTINUA EVOLUZIONE , Congresso Regionale AMD - SID Umbria 2022 Assisi - 18 /19 novembre 2022


Androgen receptor
GnRH
pituitary
LH, FSH
DHT
5αR1 & 2
7%
Free Testosterone
Testosterone + SHBG
Testosterone
testis
aromatase
0,2%
mood
voice
skin
sperms
muscle
erythrocytes
male extenal & internal genitalia
skeleton
ERα and ERβ
estrogens

A Perspective on Middle-Aged and Older Men With Functional Hypogonadism: Focus on Holistic Management

Mathis Grossmann[1,2] and Alvin M. Matsumoto[3,4]

[1]Department of Medicine, Austin Health, University of Melbourne, Heidelberg, Victoria 3081, Australia; [2]Endocrine Unit, Austin Health, Heidelberg, Victoria 3052, Australia; [3]Division of Gerontology and Geriatric Medicine, Department of Medicine, University of Washington School of Medicine, Seattle, Washington 98195; and [4]Geriatric Research, Education and Clinical Center, Seattle, Washington 98108

«Functional hypogonadism (also referred to as late-onset, age-related or adult-onset hypogonadism) is defined as the coexistence of androgen deficiency-like features and low serum T concentrations occurring in the absence of both intrinsic structural hypothalamic-pituitary-testis (HPT) axis pathology and of specific pathologic conditions suppressing the HPT axis (such as microprolactinoma, endogenous Cushing syndrome) in middle-aged or older men (≥ 50 years)»

«The community prevalence estimates of potentially functional hypogonadism in middle-aged and older men vary from 2.1% to 12.3%».

FUNCTIONAL HYPOGONADISM (or LOH

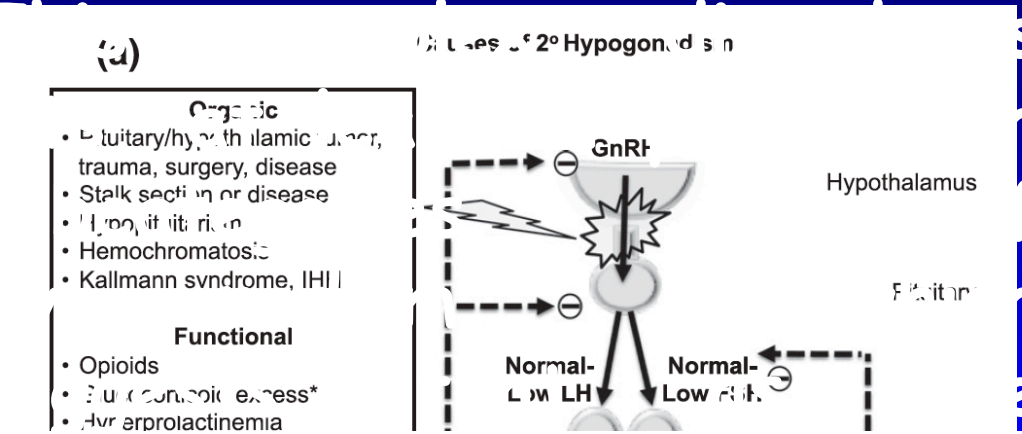
CLINICAL RESEARCH ARTICLE

A Perspective on Middle-Aged and Older Men With Functional Hypogonadism: Focus on Holistic Management

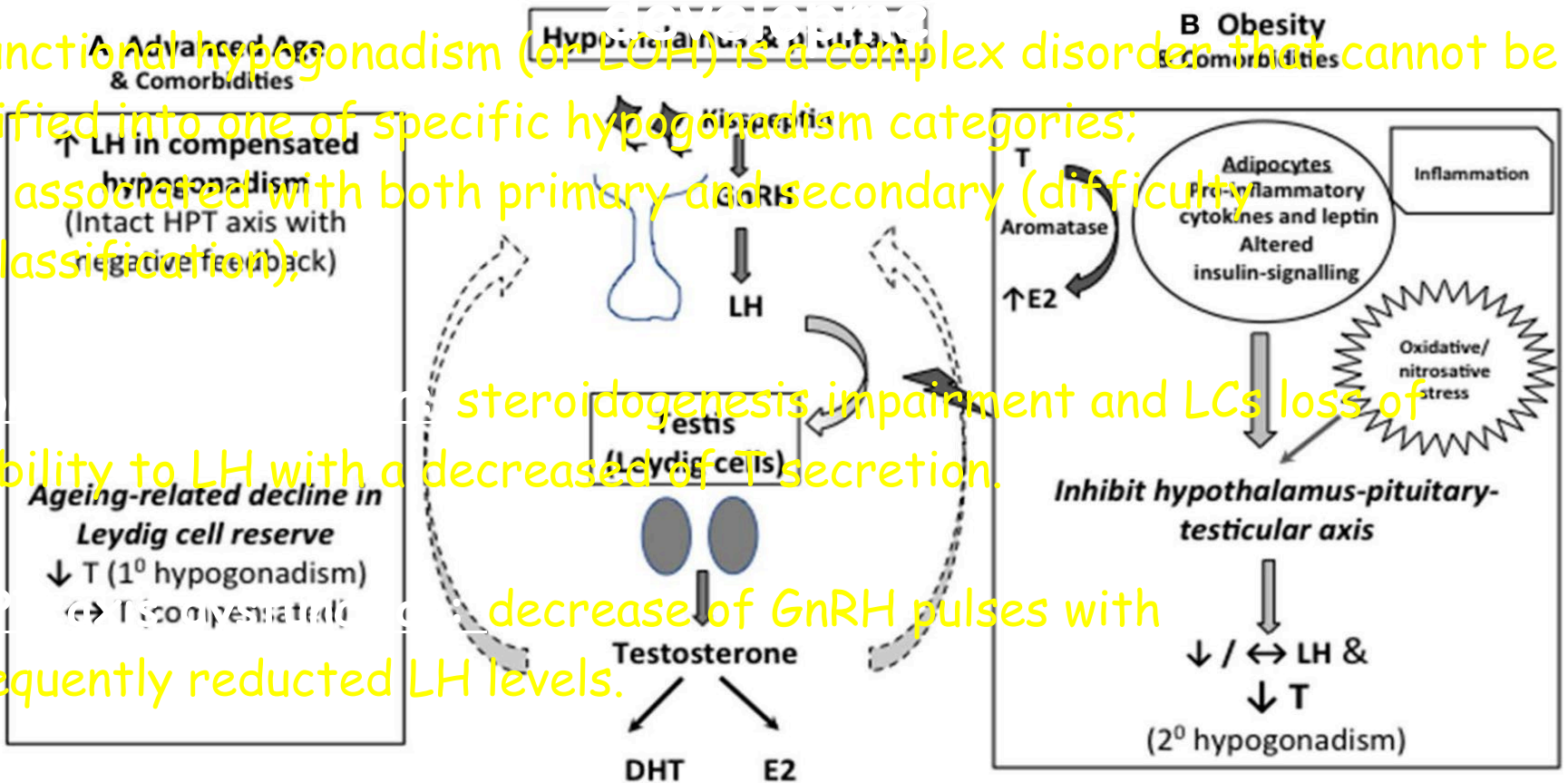
J Clin Endocrinol Metab, 2017

Mathis Grossmann[1,2] and Alvin M. Matsumoto[3,4]

[1]Department of Medicine, Austin Health, University of Melbourne, Heidelberg, Victoria 3081, Australia; [2]Endocrine Unit, Austin Health, Heidelberg, Victoria 3052, Australia; [3]Division of Gerontology and Geriatric Medicine, Department of Medicine, University of Washington School of Medicine, Seattle, Washington 98195; and [4]Geriatric Research, Education and Clinical Center, Seattle, Washington 98108



- Functional hypogonadism (or LOH) is a complex disorder that cannot be classified into one of specific hypogonadism categories;
- Is associated with both primary and secondary (difficulty for classification);



steroidogenesis impairment and LCs loss of sensibility to LH with a decreased of T secretion.

decrease of GnRH pulses with consequently reducted LH levels.

FUNCTIONAL HYPOGONADISM (or LOH)

Symtoms and Signs

TABLE 1 Symptoms and signs that may be associated with functional hypogonadism

Received: 3 February 2020 | Accepted: 4 February 2020

DOI: 10.1111/andr.12770

ANDROLOGY

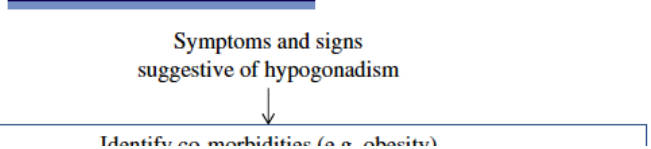
REVIEW ARTICLE

European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males

Endorsing organization: European Society of Endocrinology

Giovanni Corona[1] | Dimitrios G. Goulis[2] | Ilpo Huhtaniemi[3,4] | Michael Zitzmann[5] | Jorma Toppari[4,6] | Gianni Forti[7] | Dirk Vanderschueren[8] | Frederick C. Wu[9]

- Increased body fat/reduced muscle mass
- Osteoporosis/low bone density
- Central obesity



Society, year	Target
American Urological Association, 2018[6]	In the middle tertile of the normal reference range (15.6-20.8 nmol/L; 450-600 ng/dL)
British Society for Sexual Medicine, 2017[7]	In the mid to upper range for healthy young men (15-30 nmol/L; 433-865 ng/dL)
Canadian Medical Association, 2015[8]	In the mid-normal range for healthy young men (14-17.5 nmol/L; 404-505 ng/dL)
Endocrine Society, 2018[9]	In the mid-normal range for healthy young men (9.2-31.8 nmol/L; 264-916 ng/dL)
Endocrine Society of Australia, 2016[10,11]	In the lower part of the reference interval for eugonadal men (not reported)
European Academy of Andrology, 2020[12]	In the mid-normal range for young men (9.6-30 nmol/L; 280-873 ng/dL)
European Association of Urology, 2020[13]	The average normal range for young men (9.6-30 nmol/L; 280-873 ng/dL)
International Consultation for Sexual Medicine, 2019[14]	Not reported
International Society for the Study of Aging Male, 2015[15]	In the normal range (not reported)

TRT trial

FUNCTIONAL HYPOGONADISM (or LOH

Terapia

Formulation	Delivery system	Doses	Starting doses	Application site	Dose range	Advantages	Disadvantages	Testosterone levels monitoring
Testosterone gel 2%	Pump	10 mg/actuation; 23 mg/actuation	4 actuations/d (for 10 mg pump); 1 actuation/d (for 23 mg pump)	Shoulders, upper arms or thighs	10-70 mg daily (for 10 mg pump); 23 to 69 mg daily (for 23 mg pump)	Self-administration; quick reversal; less serum testosterone level fluctuation	Daily administration; skin irritation; second transfer	14 d after initiation, 2-4 h after actuation
Testosterone solution 2%	Pump	30 mg/actuation	1 actuation for each axilla	Axilla	30-120 mg daily	Quick reversal; good skin tolerability	Suboptimal response; secondary transfer	14 d after initiation, 2 to 8 h after dose application
Intramuscular								
Testosterone cypionate	Injection	Vial 100 mg/mL; vial 200 mg/mL	1 vial 100 mg/wk or 1 vial 200 mg/2 wk	Gluteal muscle or lateral upper thigh	50-200 mg every 7 or 14 d	Affordable cost; short acting that allows drug withdrawal in case of side effects	Multiple injections; fluctuation in serum testosterone levels	1 wk after injection
Testosterone enanthate	Injection	Vial 100 mg/mL vial 200 mg/mL; vial 250 mg/mL	1 vial every 2 or 3 wk	Gluteal muscle or lateral upper thigh	100-300 mg every 2 or 3 wk	Affordable cost; short acting that allows drug withdrawal in case of side effects	Multiple injections; fluctuation in serum testosterone levels	1 wk after injection
Testosterone propionate	Injection	Vial 100 mg/mL	½ vial every 3-5 d	Gluteal muscle or lateral upper thigh	NS	Affordable cost; short acting that allows drug withdrawal in case of side effects	Multiple injections; fluctuation in serum testosterone levels	NS
Testosterone ester combinations	Injection	Vial 250 mg/mL	1 vial every 3 wk	Gluteal muscle or lateral upper thigh	NS	Affordable cost; short acting that allows drug withdrawal in case of side effects	Multiple injections; fluctuation in serum testosterone levels	NS
Testosterone undecanoate	Injection	Vial 1000 mg/4 mL; vial 750 mg/3 mL	1 vial 1000 mg at weeks 0, 6 and every 10 to 14 wk; 1 vial 750 mg at weeks 0, 4 and every 10 wk	Gluteal muscle	1000 mg; 750 mg	Steady-state serum testosterone levels without fluctuation, few injections/year	Intramuscular injection; high cost, long acting that cannot allow drug withdrawal in case of side effects	Prior to each subsequent injection

Abbreviations: HPG, hypothalamic-pituitary-gonadal axis; NS, not specified.

IS LOH A METABOLIC DISEASE?

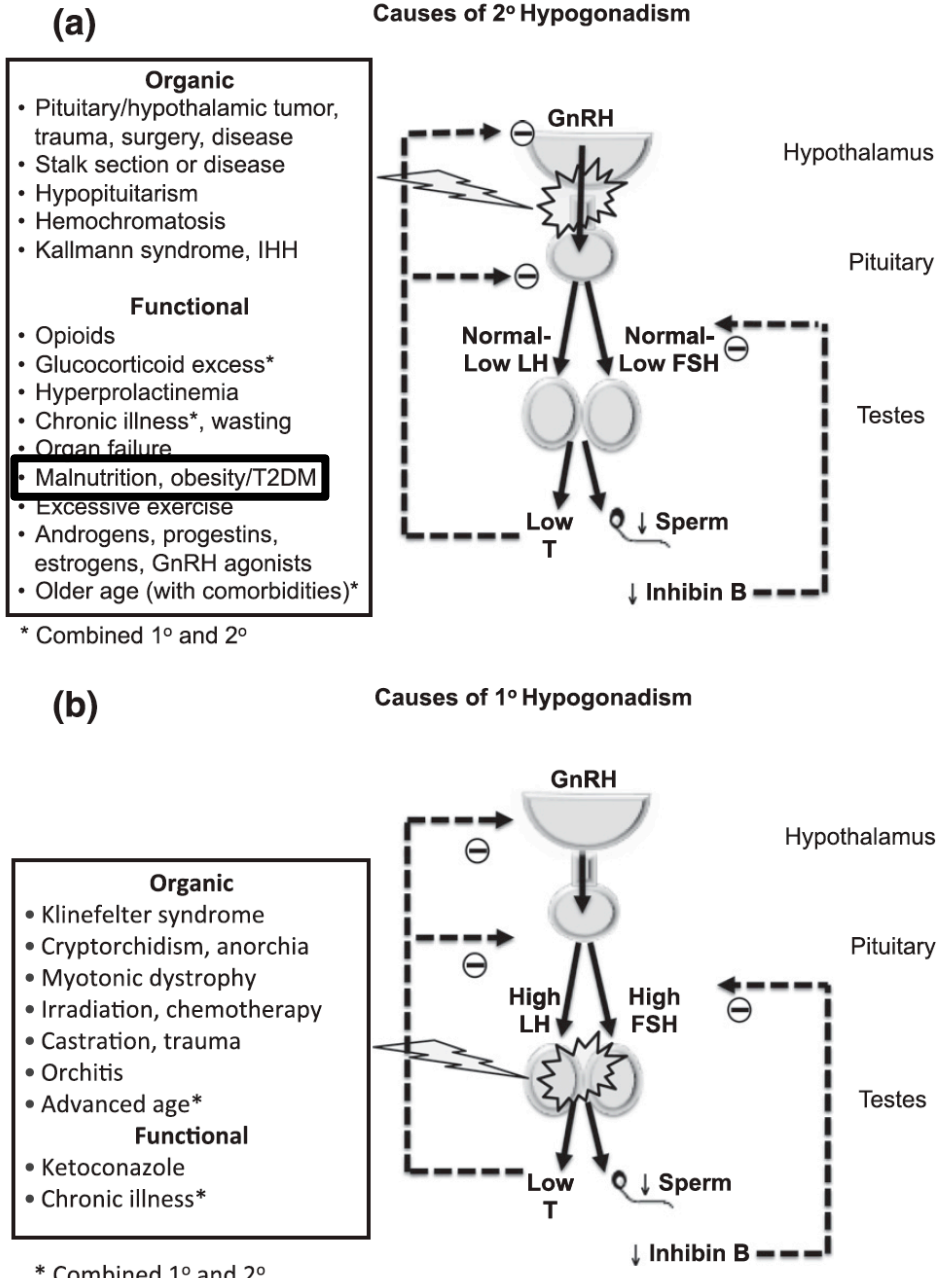
CLINICAL RESEARCH ARTICLE

A Perspective on Middle-Aged and Older Men With Functional Hypogonadism: Focus on Holistic Management

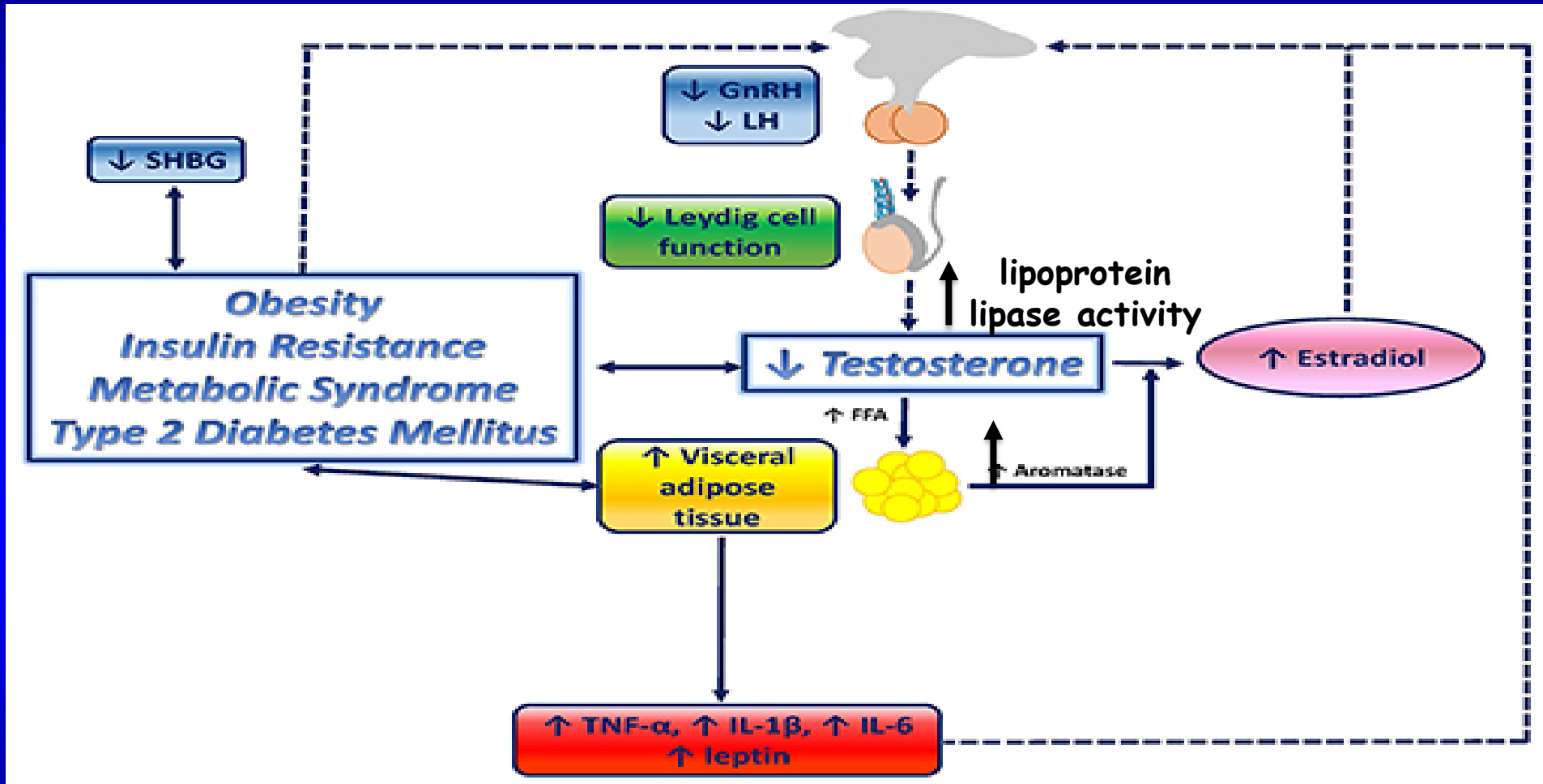
J Clin Endocrinol Metab, 2017

Mathis Grossmann[1,2] and Alvin M. Matsumoto[3,4]

[1]Department of Medicine, Austin Health, University of Melbourne, Heidelberg, Victoria 3081, Australia; [2]Endocrine Unit, Austin Health, Heidelberg, Victoria 3052, Australia; [3]Division of Gerontology and Geriatric Medicine, Department of Medicine, University of Washington School of Medicine, Seattle, Washington 98195; and [4]Geriatric Research, Education and Clinical Center, Seattle, Washington 98108

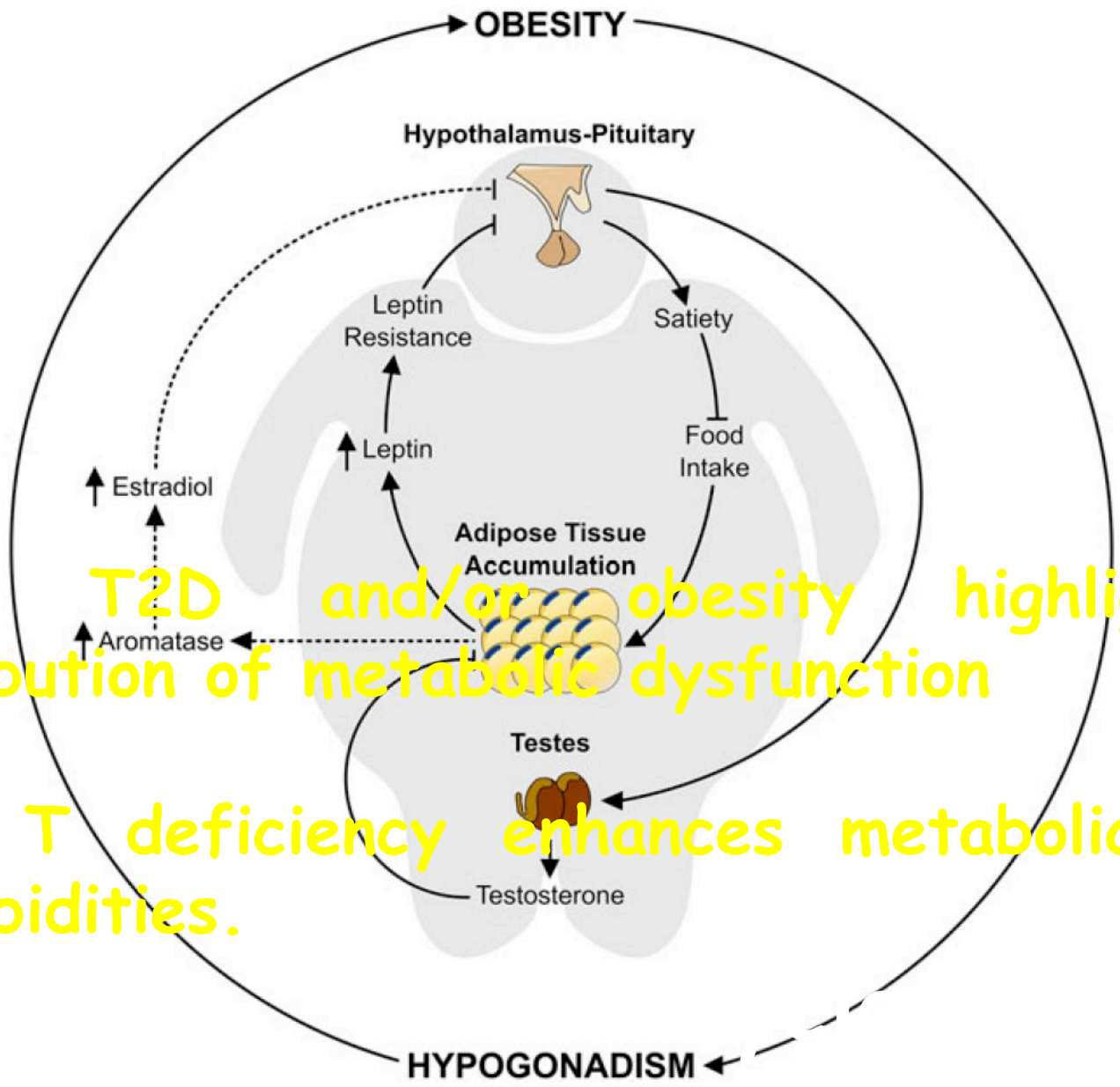


IS LOH A METABOLIC DISEASE?



Bidirectional link between metabolic impairment and hypogonadotropic hypogonadism

IS LOH A METABOLIC DISEASE?



Agi… T2D and/or obesity highlights the contribution of metabolic dysfunction

LOH… T deficiency enhances metabolic diseases comorbidities.

OBESITY AND HYPOGONADISM

Table II Characteristics of the studies about MOSH and associated traits included in meta-analyses and in the descriptive review.

Author (year)	Country	Criteria for MOSH	*n*	Age (years)	BMI (kg/m^2)	MOSH		Follow-up (months)	Q-Index
						Before surgery	After surgery		
Calderon *et al.* (2014)	Spain	↓TT and/or FT	35	39 ± 9	47.2 ± 7.7	25/35	0/25	12 ± 6	8
Calderon *et al.* (2016)	Spain	↓TT and/or FT	100	40 ± 10	46.7 ± 6.9	45/100	NA	NA	8
Mihalca *et al.* (2014)	Romania	↓TT	28	43 ± 10	50.1 ± 11.1	16/28	3/16	6	8
Mora *et al.* (2013)	Spain	↓TT	39	44 ± 10	46.9 ± 7.8	28/39	4/28	12	8
Pellitero *et al.* (2012)	Spain	↓TT and/or FT	33	41 ± 10	50.3 ± 6.1	27/33	5/27	12	8
Samavat *et al.* (2014)	Italy	↓TT	83	42 ± 11	46.7 ± 6.9	68/83	NA	6	8
Woodard *et al.* (2012)	US	↓TT	64	48 ± 10	48.2 ± 12.0	33/64	6/33	12	8

Data are means ± SD or counts. FT, free testosterone; TT, total testosterone; MOSH, male obesity-associated secondary hypogonadism.

DIABETES AND HYPOGONADISM (Prevalence)

43% of T2D patients

	Type 1 diabetes (n = 69)	All type 2 diabetes (n = 574)	Type 2 diabetes follow-up (n = 262)
Median TT (nmol/liter)	15.8 (7.6–30)	10.5 (0.3–28)	10.5 (0.8–25)
Low TT (<10 nmol/liter) (%)	7%	43%	42%
Median cFT (nmol/liter)	0.71 (0.1–0.99)	0.22 (0.0–0.55)	0.22 (0.0–0.47)
Low cFT (<0.23 nmol/liter) (%)	20%	57%	60%
Age (yr)	45 ± 1	65 ± 1	65 ± 1
Duration of diabetes (yr)	25 (1–55)	10 (0.1–44)	9.5 (1–33)
BMI (kg/m^2)	27 ± 1	30 ± 1	30 ± 1
HbA_{1c} (%)	8.0 ± 0.1	7.5 ± 0.1	7.6 ± 0.1
Fasting glucose (mmol/liter)	10.5 (2.1–20)	8.1 (2.3–24)	8.6 (2.6–22)
Antihypertensive therapy (%)	36%	80%	78%
RAS blockade (%)	32%	70%	68%
Blood pressure (mm Hg)	136/78	143/78	142/79
hs-CRP (IU/ml)	1.5 (0.2–11.5)	3.0 (0.2–192)	2.9 (0.2–58)
Lipid-lowering therapy (%)	28%	62%	60%
Triglycerides (mmol/liter)	1.1 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
Total cholesterol (mmol/liter)	4.8 ± 0.1	4.3 ± 0.1	4.5 ± 0.1
HDL cholesterol (mmol/liter)	1.7 ± 0.1	1.3 ± 0.1	1.4 ± 0.1
Chronic kidney disease (%)	43%	44%	45%
Macrovascular disease (%)	16%	42%	40%

In particular:

- Age < 40: 20%;
- Age 40-49: 29%;
- Age 50-59: 37%;
- Age 60-69: 43%;
- Age 70-79: 46%;
- Age ≥80 or older: 61%.

IS TRT AN EFFECTIVE THERAPY FOR TREATING METABOLIC DISTURBANCES

IS
TREA
OR
ES?

4.3.2 | Evidence

The metabolic effects of TRT in men with T2DM and MetS are conflicting. Only few placebo-controlled RCTs specifically investigated metabolic outcomes as primary endpoint of TRT in these populations. The TIMES-2, the largest study on T2DM or MetS subjects (n = 220), was unable to document a significant reduction in haemoglobin A_{1c} (HbA_{1c}) concentrations or BMI after 26 weeks of T gel 1%, although some improvement in the homeostatic model assessment of insulin resistance (HOMA-IR) was observed.[61] The largest RCT conducted exclusively in 199 men with T2DM was the BLAST study.[62] Long-acting injectable TU for 30 weeks resulted in significant improvement of HbA_{1c} concentrations, particularly in poorly controlled men (baseline HbA_{1c} ≥ 58 mmol/mol; 7.5%). Waist circumference decreased without any modification of BMI.[62] In contrast, Gianatti et al[63] did not observe any improvement in HbA_{1c} concentrations or HOMA-IR index in 88 men with T2DM, despite an improvement of body composition (reduction of fat mass and increase in lean mass), after 40 weeks of long-acting injectable TU when compared to placebo. Uncontrolled registry studies suggest that TU treatment may improve glycometabolic controls in men with T2DM and MetS up to 8 years[64-67] and prevents pre-diabetes progression toT2DM in men with hypogonadism.[68] The unconfirmed results of these studies have important limitations as mentioned earlier and cannot therefore be accepted as generalizable evidence. The effects of TRT on other parameters of MetS such as lipid profile and blood pressure are inconsistent.

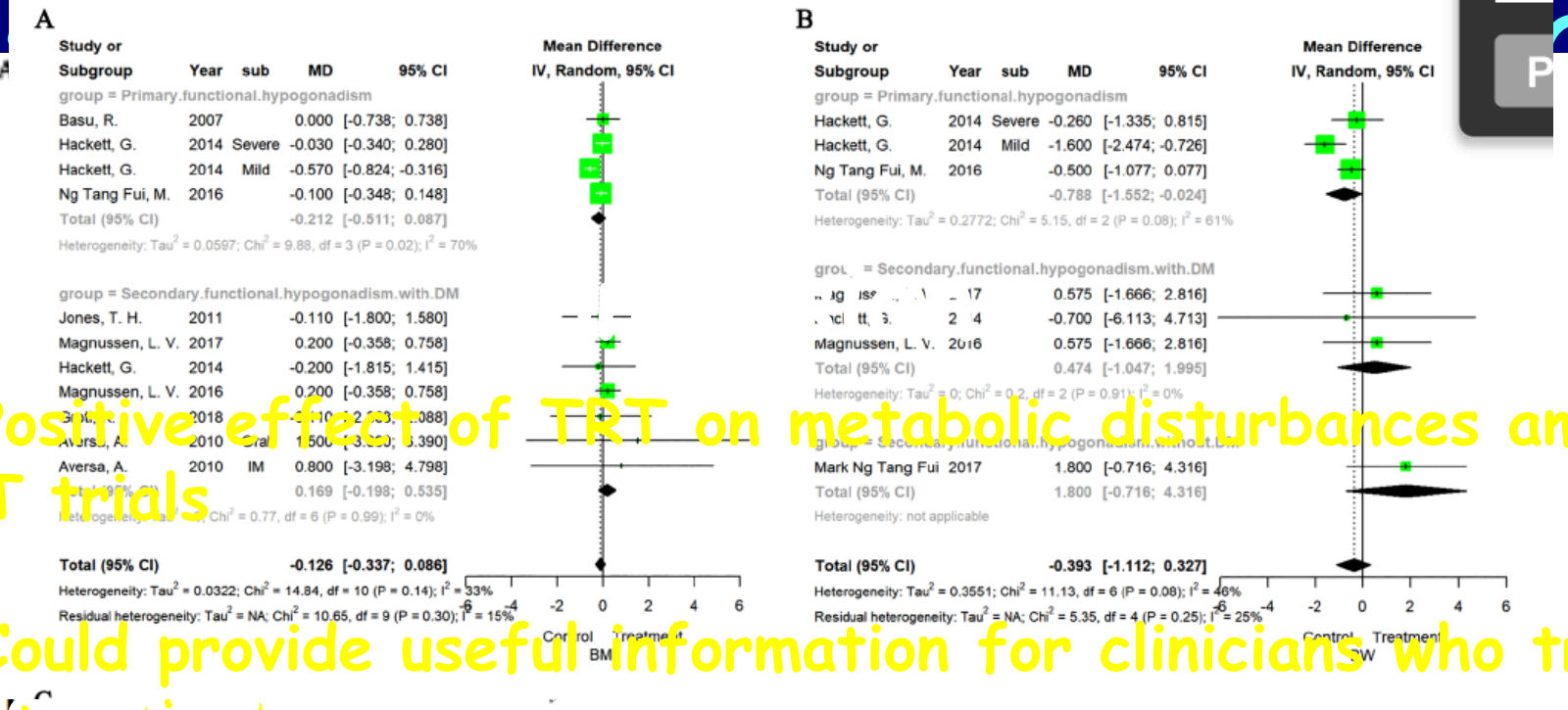
Received:
DOI: 10.11

REVIE

Eurc
inve
hypo

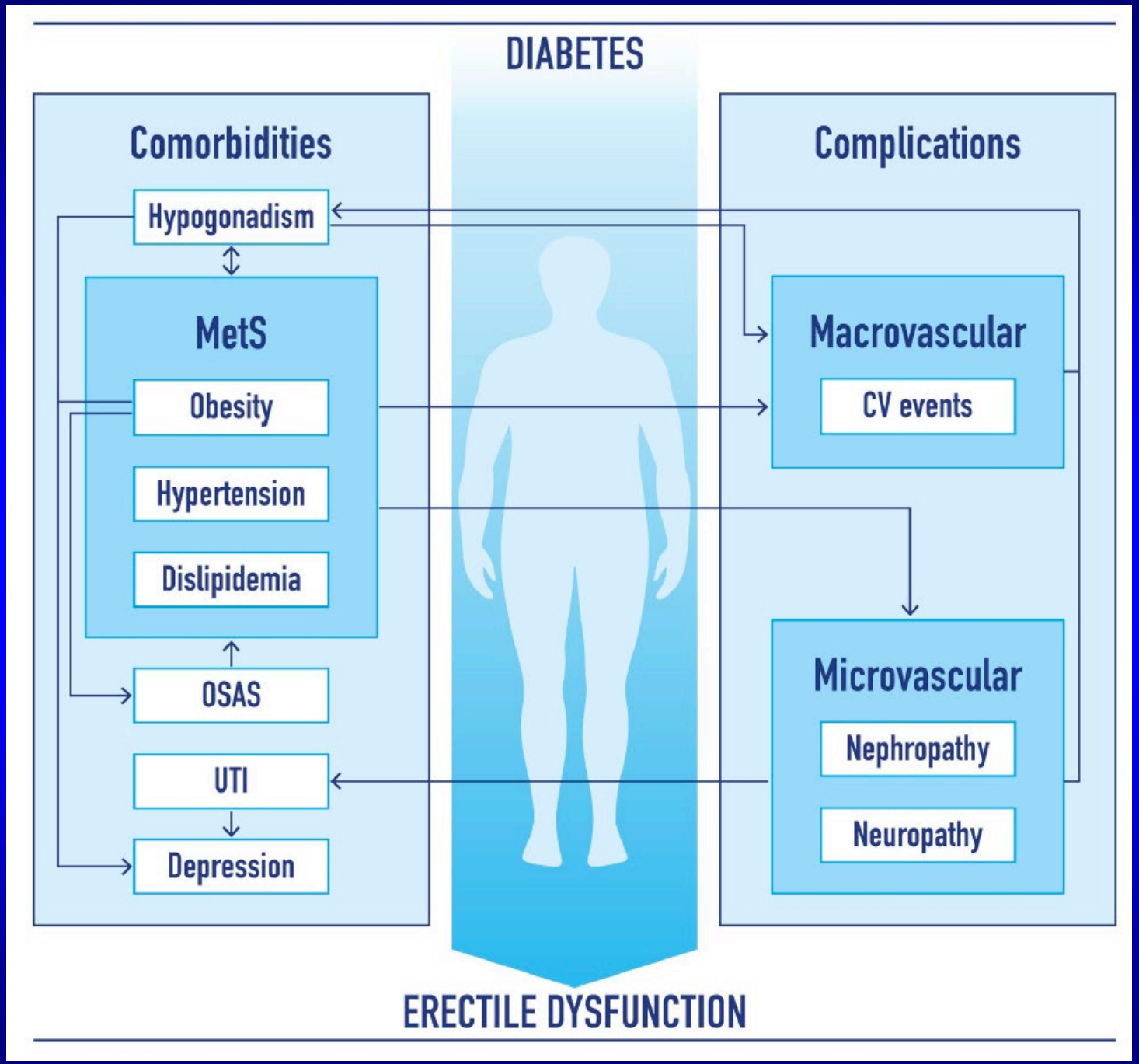
Endor

Giovar
Jorma



- Positive effect of TRT on metabolic disturbances among RCT trials
- Could provide useful information for clinicians who treat LOH patients.
- It also gives guidance for individual personalized treatment
- Proper guidance could prevent both overprescribing and passive treatment of TRT

care of LOH patients.


DIABETES
Comorbidities
Hypogonadism
MetS
Obesity
Hypertension
Dislipidemia
OSAS
UTI
Depression
Complications
Macrovascular
CV events
Microvascular
Nephropathy
Neuropathy
ERECTILE DYSFUNCTION

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION VOLUME 45 | SUPPLEMENT 1

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2022*

"Mean levels of testosterone are lower in men with diabetes compared with age-matched men without diabetes, but obesity is a major confounder…

Testosterone replacement in men with symptomatic hypogonadism may have benefits including improved sexual function, well-being, muscle mass and strength, and bone density…

Low Testosterone in Men

Recommendation

4.11 In men with diabetes who have symptoms or signs of hypogonadism, such as decreased sexual desire (libido) or activity, or erectile dysfunction, consider screening with a morning serum testosterone level. **B**

Erectile Dysfunction

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve the patient's quality of life.

E. DISFUNZIONE ERETTILE

La disfunzione erettile (DE) ha un valore predittivo per evento cardiovascolare (CV) uguale o maggiore di altri fattori di rischio tradizionali quali la familiarità per cardiopatia ischemica, il fumo di sigaretta o la dislipidemia. III A

La valutazione della DE deve includere il suo grado di severità dal momento che questa si associa a maggior rischio di eventi CV maggiori, all'estensione della cardiopatia ischemica e al rischio di arteriopatia obliterante. *III A*

La presenza di DE nel diabete tipo 2 va ricercata già alla diagnosi e poi rivalutata una volta l'anno. Nel diabete tipo 1 la DE va ricercata in presenza di una lunga durata di malattia (>10 anni) o di complicanze croniche, in particolare neuropatia e vasculopatia. *IV B*

La presenza di DE impone la necessità di instaurare un percorso diagnostico composto da:

- Anamnesi;
- Obiettività;
- Esami di laboratorio specifici (testosterone totale, SHBG, prolattina, TSH, PSA).
- La valutazione dell'ecodoppler penieno eseguita in condizioni di flaccidità e/o dopo stimolo con prostaglandina E1 (PGE1) può essere di aiuto per identificare pazienti a più alto rischio cardiovascolare. *VI B*

Non sono in genere necessarie altre indagini a meno che non si preveda la necessita di intervenire chirurgicamente. *VI B*

In presenza di ipogonadismo (livelli di testosterone totale < 3.5 ng/ml o 12 nmol/L o testosterone libero calcolato < 225 pmol/L), una volta confermato anche eseguendo un dosaggio di LH, è necessario instaurare un terapia sostituiva a base di testosterone, se non sono presenti controindicazioni. *I A*

Il trattamento medico prevede l'utilizzo dei farmaci inibitori della PDE-5 (sildenafil, vardenafil, tadalafil, avanafil) tenendo in considerazione le specifiche caratteristiche farmacocinetiche, le esigenze della coppia e la presenza di farmaci e patologie associate. *I A*

Il calo ponderale, l'attività fisica ed il miglioramento del controllo glicemico possono essere d'aiuto. *VI B*