Οι Τελευταίες Οδηγίες για την Αντιμετώπιση του Υπογοναδισμού της EAU

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Conflict of interest

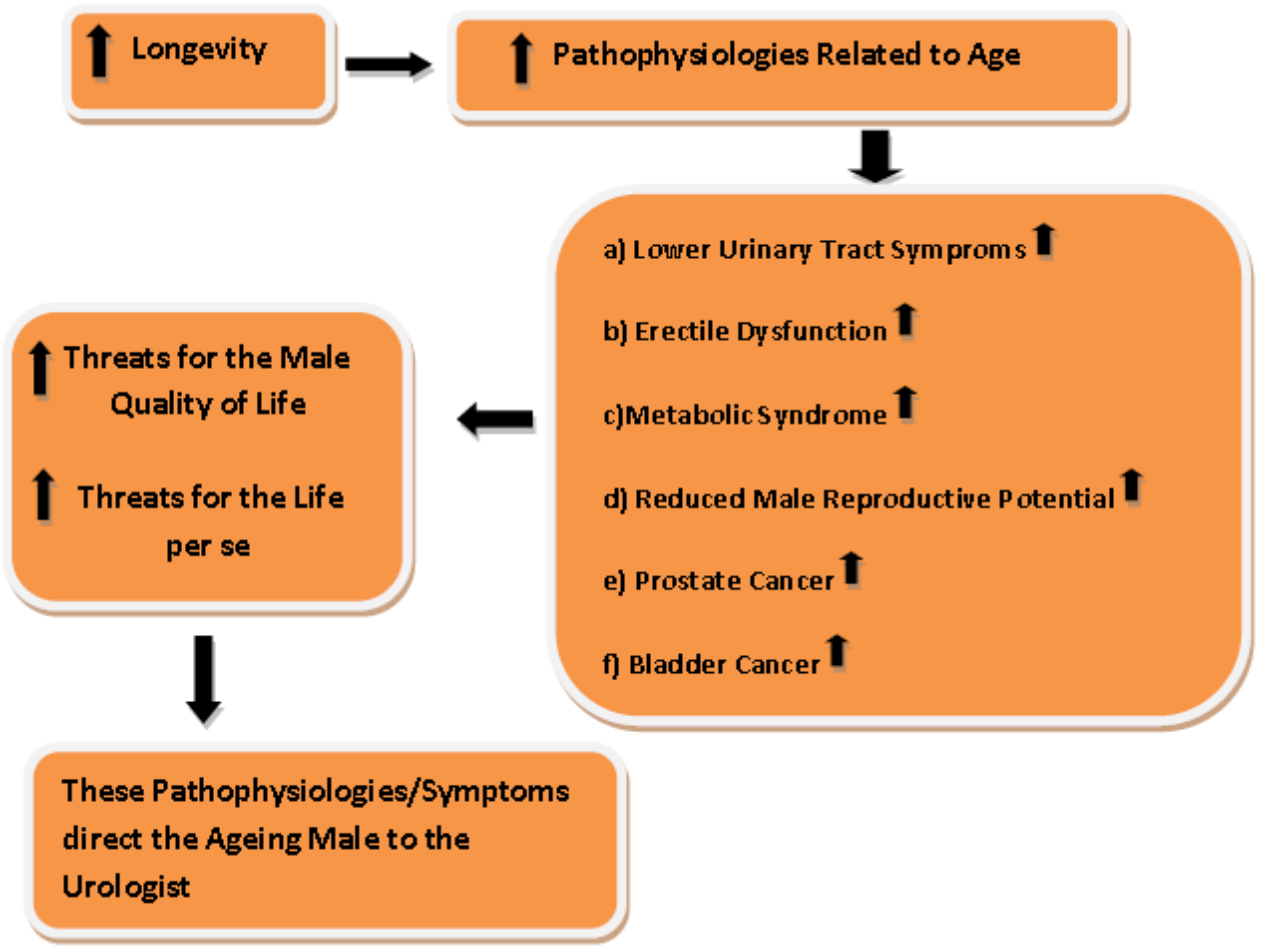
TESTOSTERONE REPLACEMENT TREATMENT IN THE AGING MALE: WHO TAKES THE LEAD?

INCREASE IN LONGEVITY GIVES THE FIRST LEAD TO THE UROLOGIST

Health and Quality of Life Features are Related with Age-Dependent Pathophysiologies of the Urogenital Tract

- According to World Health Organization in Europe in the year 2015 the life expectancy for males has reached the level of 73.2 years.
- ***World health statistics 2016: monitoring health for the SDGs. Published by WHO Pres, pp 1-126***

INCREASE IN LONGEVITY GIVES THE FIRST LEAD TO THE UROLOGIST



INCREASE IN LONGEVITY GIVES THE FIRST LEAD TO THE UROLOGIST

- **Age-Dependent Pathophysiologies Direct the Male to Visit the Urologist**
- Several of the above symptoms/diseases are unequivocally related to peripheral serum testosterone levels. Looking at the frequency or the clinical relevance of each of the above symptoms/pathophysiologies in various ages, their relationship with the age becomes evident .

THE UROLOGIST IS THE APPROPRIATELY TRAINED PHYSICIAN TO TAKE CARE OF THE AGEING MALE

Lower Urinary Tract Symptoms

- Lower urinary tract symptoms are evident in 72.3% of men with age larger than 50 years. It has been indicated that the clinical relevance is present in about 50% of men with lower urinary tract symptoms.

BJU Int., 2009 , 103:24-32, BJU Int., 2009, 104:352-60

- Strong evidence has been provided indicating vividly a negative effect of lower urinary tract symptoms across several domains of urinary-specific-health-related quality of life and on the overall perception of bladder problems, general health status, and mental health .

BJU Int., 2009, 103: 4-11

ERECTILE DYSFUNCTION

Erectile Dysfunction

Male Age (years)	Frequency of erectile dysfunction
<40	1% – 10 %
40-49	15%
50-59	30%
60-69	40%
70-80	50% - 100%

JSM, 2010, 7:1598-607

- Sexual health is a crucial aspect of overall health and quality of life.

J Sex Med 2010; 7:3572–88

- It has been demonstrated very vividly that interaction between erectile dysfunction and depression results in an impaired quality of life attributable to a decrease in free testosterone serum levels.

Int J Impot Res. 2016, ijir.2016.49

- The decrease in testosterone levels is one of the causes of erectile dysfunction and low sexual desire.

Aging Male, 2016, 254-258

Metabolic Syndrome

- The frequency of metabolic syndrome is known to increase with the age. In EMAS, 30.5 % of patients have demonstrated metabolic syndrome (40 to 79 years) at the time of inclusion. In addition during the follow up period of 4.3 years, another percentage equal to 18% developed metabolic syndrome.

J Clin Endocrinol Metab, 2016, 101:2647-57

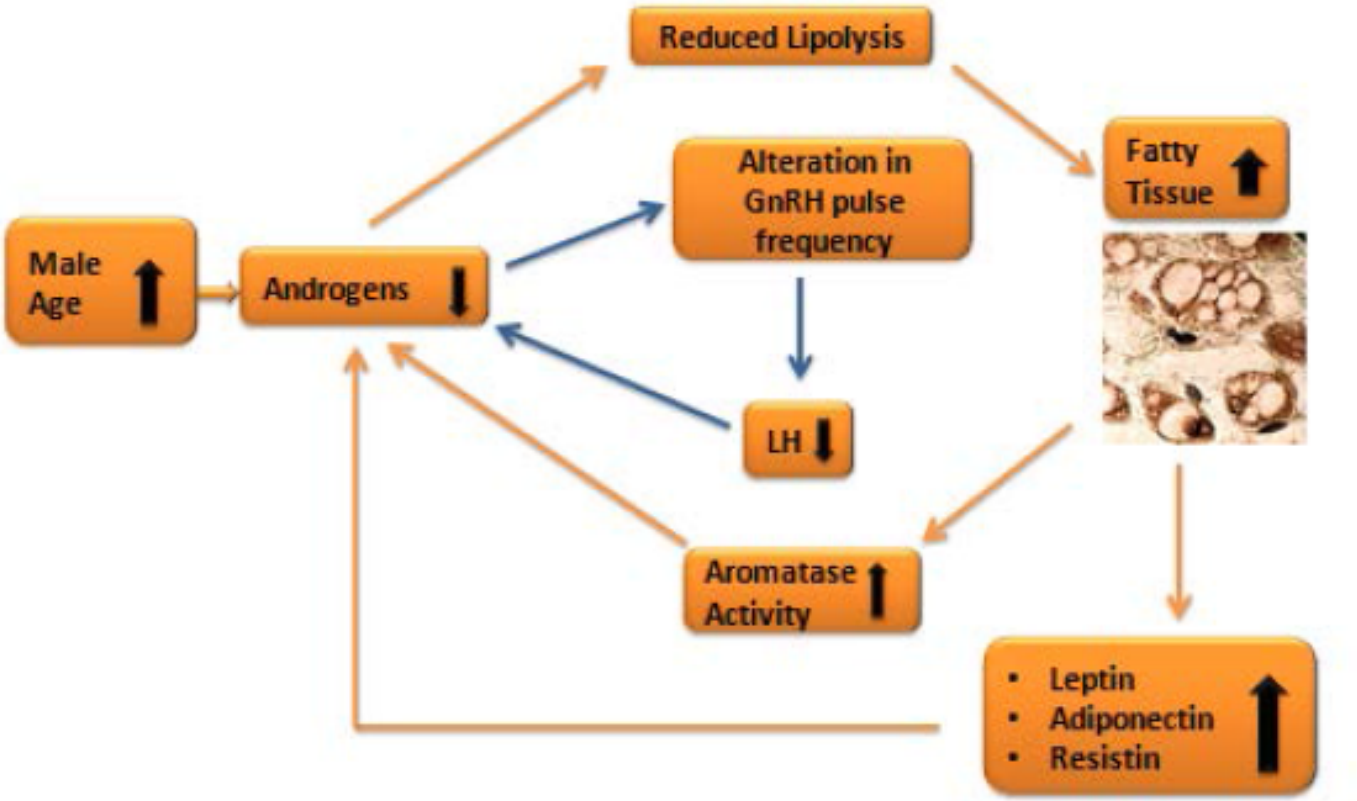
- Several studies have indicated a link between low serum total testosterone levels and the presence of metabolic syndrome.

Aging Male, 2016, 19:85-9

- In fact, subnormal peripheral serum testosterone levels in an ageing male could cause/aggreviate the symptoms of metabolic syndrome (i.e., sexual function disorders, reduced fertility or disorders of the prostate) that direct the male to visit the urological office.

Metabolic Syndrome

Cascade of biochemical events responsible for the development of a vicious cycle between low serum testosterone levels and increase in fatty tissue.



MALE REPRODUCTIVE POTENTIAL

Decreased Male Reproductive Potential

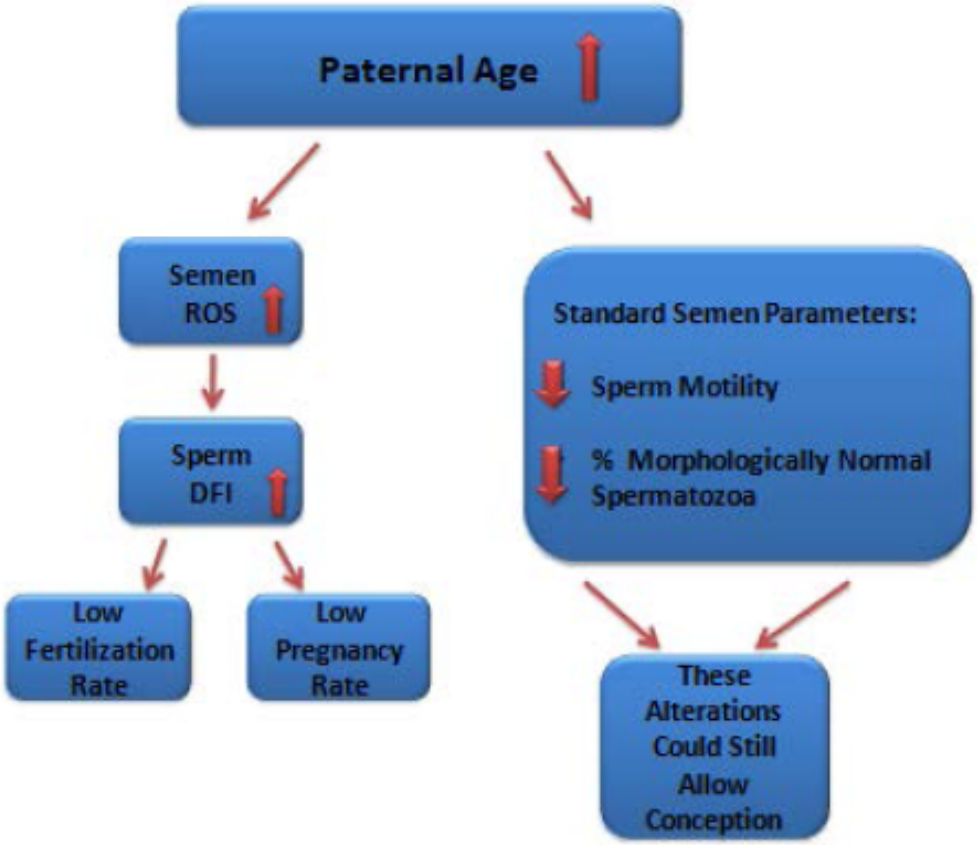
- Nowadays the percentage of divorced males is increasing and the age of marriage in the male becomes elevated, especially in western countries. Thus a significant subpopulation of ageing males attempt to father his own child.
- It is evident that the role of urologist
  - to assist ageing males to achieve paternity and to
  - ameliorate any age-dependent declines in semen quality is of paramount importance.
- An interesting study has demonstrated a longer time to achieve pregnancy in older fathers. Indeed, the authors reported a 5-fold increase in time to pregnancy in men over 45 years.

Fertil Steril. 2003; 79:1520–7

MALE REPRODUCTIVE POTENTIAL

MALE REPRODUCTIVE POTENTIAL

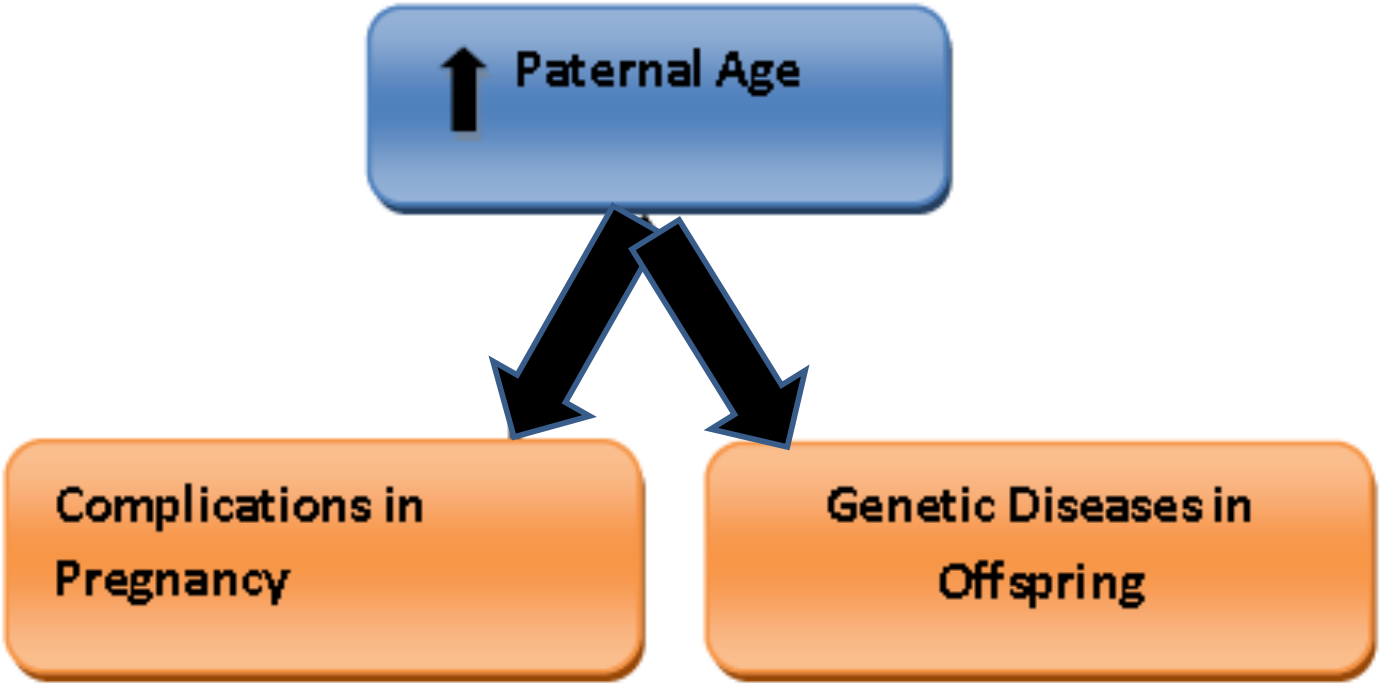
Rationale for impaired pregnancy rates in ageing males.



ROS: Reactive oxygen species

DFI: DNA Fragmentation Index

MALE REPRODUCTIVE POTENTIAL



TRT IN PATHOPHYSIOLOGIES/SYMPTOMS ATTRIBUTED TO A DECREASE IN T GIVES ANOTHER LEAD TO THE UROLOGIST

Low peripheral serum testosterone levels can give rise to/aggreviate medical conditions/symptoms such as:

- Delayed puberty
- Small testes
- Male-factor infertility
- Decreased body hair
- Gynaecomastia
- Decrease in lean body mass and muscle strength
- Visceral obesity
- Decrease in bone mineral density (osteoporosis) with low trauma fractures
- Reduced sexual desire and sexual activity
- Erectile dysfunction
- Fewer and diminished nocturnal erections
- Hot flushes
- Sarcopenia
- Changes in mood, fatigue and anger
- Sleep disturbances
- Metabolic syndrome
- Insulin resistance and type 2 diabetes mellitus
- Diminished cognitive function

European Association of Urology, Guidelines on Male Hypogonadism 2015, Androgen Replacement – Indications and Principles , In Clinical Andrology. EAU/ESAU Course Guidelines,Edited by L Björndahl, A Giwercman, H Tournaye, W Weidner. Published by Informa Healthcare USA

TRT AND MALE FERTILITY POTENTIAL

Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis

Peter Y Liu, Ronald S Swerdloff, Peter D Christenson, David J Handelsman, Christina Wang, and the Hormonal Male Contraception Summit group*

Lancet 2006; 367: 1412–20

- These data represented about 90% of all published data from individuals using androgen or androgen-progestagen regimens. Multivariate Cox's analysis showed higher rates of recovery with older age, Asian origin, shorter treatment duration, shorter-acting testosterone preparations, higher sperm concentrations at baseline, faster suppression of spermatogenesis, and lower blood concentrations of luteinising hormone at baseline.

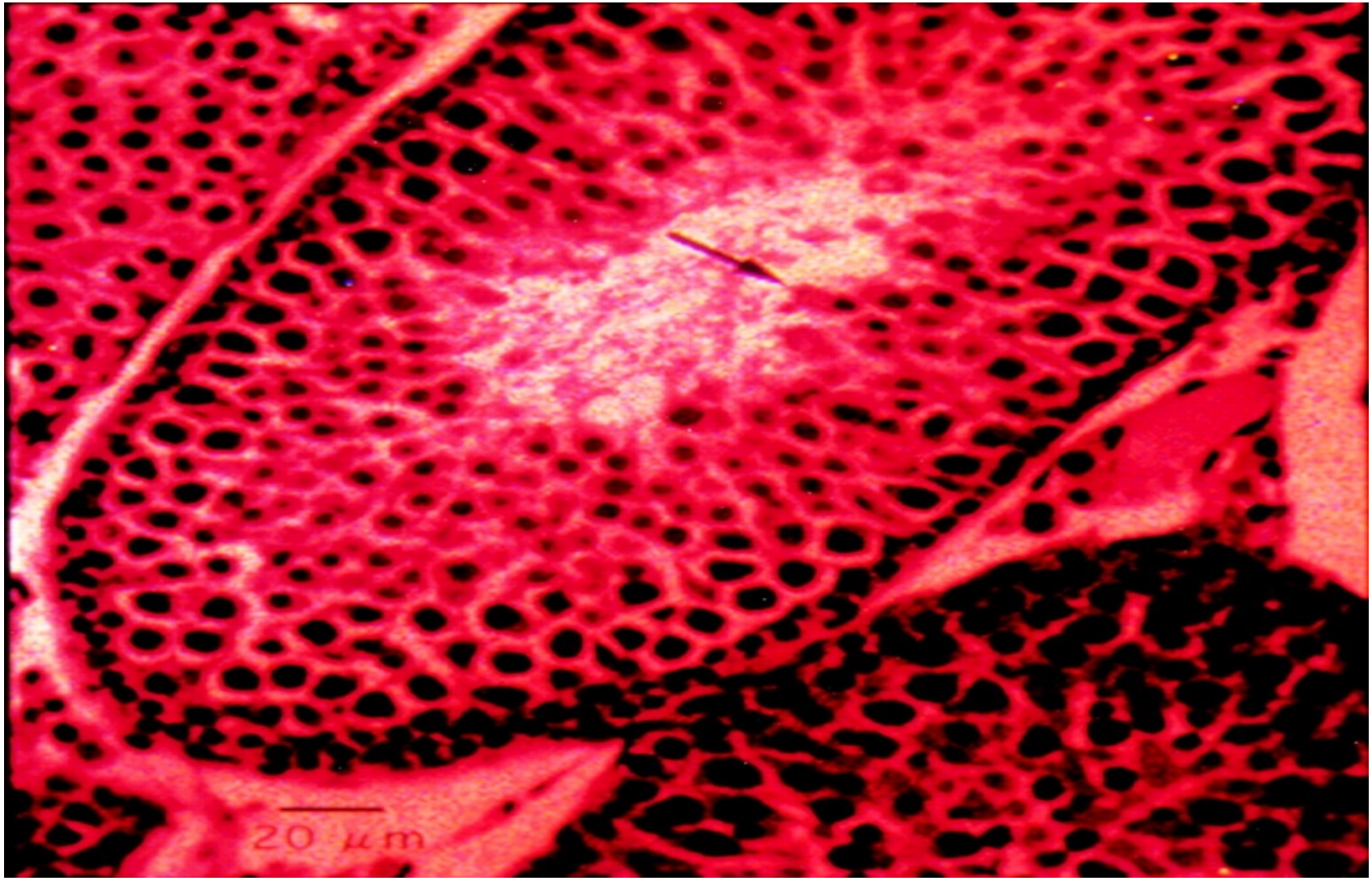
Probability of Recovery to 20 million per mL	Duration (months)
67% (61-72)	6
90% (85-93)	12
96% (92-98)	16
100%	24

Lancet 2006; 367:1412-20

Human Reproduction vol.14 no.8 pp.1998–2006, 1999

Influence of the male reproductive tract on the reproductive potential of round spermatids abnormally released from the seminiferous epithelium*

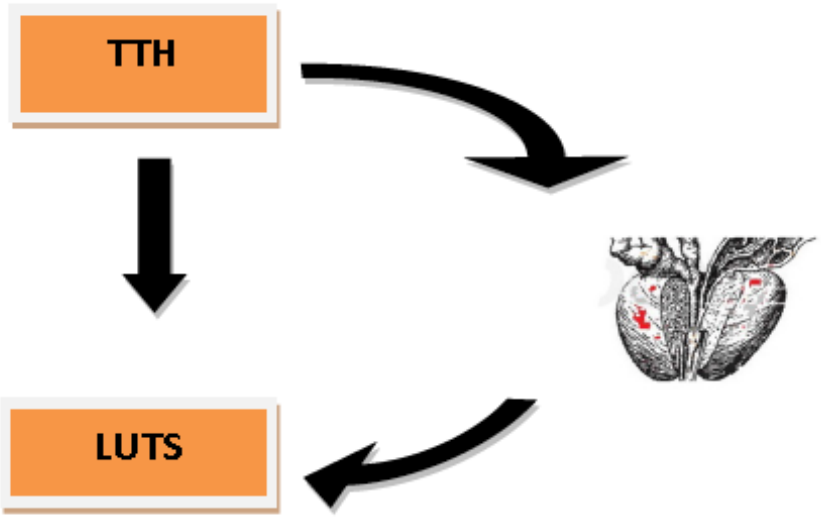
N.Sofikitis[1,3], K.Ono[1], Y.Yamamoto[1], H.Papadopoulos[2] and I.Miyagawa[1]



TRT AND LUTS

Lower urinary tract symptoms (LUTS)

- There is a general belief that TRT may exacerbate LUTS because of growth-promoting effects on the prostate.



Eur Urol 2016;69:1083-90, Urology 2016;88:22-32.

LUTS AND TRT

- In contrast, a systematic review considered data on patients with mild LUTS randomized to TRT or no treatment .
- The results demonstrated no statistically significant difference in IPSS change from baseline with an average follow-up of 34.4 months.
- Observational studies have found that long-term TRT may decrease the IPSS.

World J Urol 2014;32:1049-1054

- No data are available on TRT in men with severe LUTS (IPSS>19).

PCa AND TRT

Prostate Cancer

- The overall literature does not support a link between high intrinsic T levels and PCa.

BJUI
BJU International

Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis

Peter Boyle*,†, Alice Koechlin*,†, Maria Bota*,†, Alberto d'Onofrio†, David G. Zaridze‡, Paul Perrin§, John Fitzpatrick¶, Arthur L. Burnett** and Mathieu Boniol*,†

- Prostate cancer appears to be unrelated to endogenous testosterone levels. Testosterone replacement therapy (TRT) for symptomatic hypogonadism does not appear to increase PSA levels nor the risk of prostate cancer development

Testosterone Therapy in Men With Prostate Cancer

Alan L. Kaplan[a,*], *Jim C. Hu*[b], *Abraham Morgentaler*[c], *John P. Mulhall*[d], *Claude C. Schulman*[e], *Francesco Montorsi*[f]

EUROPEAN UROLOGY 69 (2016) 894–903

- An important paradigm shift has occurred within the field, in which testosterone therapy may now be regarded as a viable option for selected men with prostate cancer suffering from testosterone deficiency.

A New Era of Testosterone and Prostate Cancer: From Physiology to Clinical Implications

Mohit Khera [a,*], *David Crawford* [b], *Alvaro Morales* [c], *Andrea Salonia* [d], *Abraham Morgentaler* [e]

EUROPEAN UROLOGY 65 (2014) 115–123

- The long-held belief that PCa risk is related to high serum androgen concentrations can no longer be supported.
- Current evidence indicates that maximal androgen-stimulated PCa growth is achieved at relatively low serum testosterone concentrations.
- It may therefore be reasonable to consider testosterone therapy in selected men with PCa and symptomatic hypogonadism.

Metabolic Syndrome and TRT

J Sex Med. 2016 Aug;13(8):1199-211. doi: 10.1016/j.jsxm.2016.06.003.

Effects of 8-Year Treatment of Long-Acting Testosterone Undecanoate on Metabolic Parameters, Urinary Symptoms, Bone Mineral Density, and Sexual Function in Men With Late-Onset Hypogonadism.

Permpongkosol S[1], Khupulsup K[2], Leelaphiwat S[2], Pavavattananusorn S[3], Thongpradit S[4], Petchthong T[4].

- TU did not improve all obesity parameters. A statistically significant decrease was found in waist circumference, percentage of body fat, glycated hemoglobin, cholesterol, low-density lipoprotein, and International Prostate Symptom Score. TU did not produce differences in body mass index, high-density lipoprotein, triglyceride, or the Aging Male Symptoms score from baseline.

- In obese subjects with established HG, testosterone supplementation (TS) could be of help in increasing muscle strength and exercise capacity, thus improving the efficiency of lifestyle interventions, which include physical activity.

  In symptomatic, obese, hypogonadal subjects, TS can be considered. Whereas long-term studies suggest that TS could decrease weight, analysis of controlled studies only support a parallel increase in lean mass and decrease in fat mass, with a resulting null effect on weight.

  Considering that T induces an increase in muscle mass, it is conceivable that the amount of activity obese people can undertake after TS will increase, allowing a closer adherence to physical exercise programs.
- Corona et al., 2015.

Molecular and Cellular Endocrinology 418 (2015) 120–133

TRT, LIBIDO, AND ERECTILE FUNCTION

Effects of androgens on cavernosal tissue

- Regulation of nitric oxide synthase isoforms expression and activity
- Regulation of phosphodiesterase 5 expression and activity
- Regulation of smooth muscle cell growth and response to vasodilators
- Maintenance of penile neural structure and function
- Regulation of the alpha-adrenoreceptor expression and function
- Regulation of penile connective tissue metabolism
- Regulation of differentiation of progenitor vascular-stroma cells into myogenic and adipogenic lineages

Hormonal replacement and sexuality in men.

Davidson JM, Kwan M, Greenleaf WJ.

***Clin Endocrinol Metab.* 1982 Nov;11(3):599-623.**

It appears that the initial action of T may be on libido factors which lead in turn to the stimulation of other aspects of sexuality.

0022-5347/00/1642-0371/0
THE JOURNAL OF UROLOGY®

Vol. 164, 371–375, August 2000
Printed in U.S.A.

TESTOSTERONE SUPPLEMENTATION FOR ERECTILE DYSFUNCTION: RESULTS OF A META-ANALYSIS

PANKAJ JAIN, ALFRED W. RADEMAKER AND KEVIN T. MCVARY

- Transdermal testosterone therapy was more effective than intramuscular or oral treatment.
- Intramuscular and oral treatments were equivalent.
- There was a statistically significant difference in favor of testosterone over placebo, implying a role for supplementation in select groups.

The Journal of Sexual Medicine

Volume 2, Issue 4, July 2005, Pages 559–564

ORIGINAL RESEARCH—ENDOCRINE

Testosterone Therapy Can Enhance Erectile Function Response to Sildenafil in Patients with PADAM: A Pilot Study

Rany Shamloul, MD[1, 2], Hussein Ghanem, MD[1], Ibrahim Fahmy, MD[1], Amr El-Meleigy, MD[3], Shedeed Ashoor, MD[4], Abdelrahman Elnashaar, MD[1], Ihab Kamel, MD[1]

We conclude that TRT appears to be beneficial and safe in facilitating the erectile response and patient satisfaction with sildenafil in men with PADAM symptoms. Androgen supplementation should be carried out cautiously with careful monitoring to avoid possible adverse effects.

Clinical Endocrinology (2005) 63, 381–394 doi: 10.1111/j.1365-2265.2005.02350.x

ORIGINAL ARTICLE

Effects of testosterone on sexual function in men: results of a meta-analysis

Andrea M. Isidori*, Elisa Giannetta*, Daniele Gianfrilli*, Emanuela A. Greco*, Vincenzo Bonifacio*, Antonio Aversa*, Aldo Isidori*, Andrea Fabbri† and Andrea Lenzi‡

- The meta-analysis of available studies indicates that T treatment might be useful for improving vasculogenic ED in selected subjects with low or low-normal T levels.

- In patients with arteriogenic ED and low-normal androgen levels, short-term testosterone administration increases T and FT levels and improves the erectile response to sildenafil likely by increasing arterial inflow to the penis during sexual stimulation.

CLINICAL ENDOCRINOLOGY (2003) 58:632-638

Testosterone: a vascular hormone in health and disease

Daniel M Kelly[1] and **T Hugh Jones**[1,2]

Journal of Endocrinology
(2013) **217**, R47–R71

- In addition TRT has beneficial effects on erectile dysfunction due to the vasodilatory actions of testosterone (i.e., regulation of the autonomic vascular nervous system) and the restoration of normal vascular function

0013-7227/04/$15.00/0
Printed in U.S.A.

Endocrinology 145(5):2253–2263

doi: 10.1210/en.2003-1699

Androgens Regulate Phosphodiesterase Type 5 Expression and Functional Activity in Corpora Cavernosa

ANNAMARIA MORELLI, SANDRA FILIPPI, ROSA MANCINA, MICHAELA LUCONI, LINDA VIGNOZZI, MIRCA MARINI, CLAUDIO ORLANDO, GABRIELLA BARBARA VANNELLI, ANTONIO AVERSA, ALESSANDRO NATALI, GIANNI FORTI, MAURO GIORGI, EMMANUELE A. JANNINI, FABRIZIO LEDDA, AND MARIO MAGGI

European Urology

European Urology 47 (2005) 409–416

Testosterone Regulates PDE5 Expression and in vivo Responsiveness to Tadalafil in Rat Corpus Cavernosum

Xin-hua Zhang[a,1], Annamaria Morelli[a,1], Michaela Luconi[a], Linda Vignozzi[a], Sandra Filippi[b], Mirca Marini[c], Gabriella Barbara Vannelli[c], Rosa Mancina[a], Gianni Forti[a], Mario Maggi[a,*]

Journal of Gerontology: MEDICAL SCIENCES
2003, Vol. 58A, No. 12, 1103–1110

Review Article

The Mechanisms of Androgen Effects on Body Composition: Mesenchymal Pluripotent Cell as the Target of Androgen Action

Shalender Bhasin, Wayne E. Taylor, Rajan Singh, Jorge Artaza, Indrani Sinha-Hikim, Ravi Jasuja, Helen Choi, and Nestor F. Gonzalez-Cadavid

- Testosterone promotes the commitment of pluripotent stem cells into the myogenic lineage.
- Testosterone inhibits their differentiation into the adipogenic lineage.
- The hypothesis that the primary site of androgen action is the pluripotent stem cell provides a unifying explanation for the observed reciprocal effects of testosterone on muscle and fat mass.

Recommendations for screening men with adult-onset hypogonadism

Recommendations	LE	GR
Screen for testosterone deficiency only in adult men with consistent and multiple signs and symptoms listed in Table 3.	3	C
Young men with testicular dysfunction and men older than 50 years of age with low testosterone should additionally be screened for osteoporosis.	2	B

Recommendations	LE	GR
Offer men with mild/moderate symptoms, minimally bothered by their symptoms, watchful waiting.	1b	A
Offer men with LUTS lifestyle advice prior to or concurrent with treatment.	1b	A

Table 3: Causes of testicular deficiency

Factors	Causes
Congenital	Anorchia
	Testicular dysgenesis/cryptorchidism
	Genetic abnormalities (karyotype, Y-chromosome deletions)
Acquired	Trauma
	Testicular torsion
	Post-inflammatory forms, particularly mumps orchitis
	Exogenous factors (medications, cytotoxic or anabolic drugs, irradiation, heat)
	Systemic diseases (liver cirrhosis, renal failure)
	Testicular tumour
	Varicocele
	Surgery that may compromise vascularisation of the testes and lead to testicular atrophy
Idiopathic	Unknown aetiology
	Unknown pathogenesis

5.5.4 *Recommendations for hypogonadism*

Recommendations	GR
Provide testosterone replacement therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood.	A
In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (human chorionic gonadotropin(hCG), human menopausal gonadotropins (hMG), recombinant follicle-stimulating hormone (rFSH)).	A*
Do not use testosterone replacement for the treatment of male infertility.	A*

**Upgraded following panel consensus.*

5.7.2 *Recommendation for idiopathic male infertility*

Recommendations	GR
Medically treat male infertility only for cases of hypogonadotropic hypogonadism.	A
No clear recommendation can be made for treatment with gonadotropins, anti-oestrogens and antioxidants even for a subset of patients.	B

Recommendation	LE	GR
Differentiate the two forms of hypogonadism (primary and secondary hypogonadism) by determining luteinising hormone and follicle-stimulating hormone levels, as this has implications for patient evaluation and treatment and makes it possible to identify patients with associated health problems and infertility.	1b	B

Table 5: Main indications for testosterone treatment

Delayed puberty (constitutional or congenital forms (HH, Kallmann's syndrome))
Klinefelter syndrome with hypogonadism
Sexual dysfunction and low testosterone
Low bone mass in hypogonadism
Adult men with low testosterone and consistent and preferably multiple signs and symptoms of hypogonadism following unsuccessful treatment of obesity and comorbidities (listed in Table 3)
Hypopituitarism
Testicular dysfunctions and hypogonadism
Type 2 diabetes mellitus with hypogonadism

Table 6: Contraindications against testosterone treatment

Locally advanced or metastatic prostate cancer
Male breast cancer
Men with an active desire to have children
Haematocrit > 0.54
Severe chronic cardiac failure/New York Heart Association Class IV

Recommendations	LE	GR
Improve lifestyle, reduce weight in case of obesity and treat comorbidities before starting testosterone therapy.	3	C
In hypogonadal men with erectile dysfunction start with a PDE5-inhibitor as first line treatment and add testosterone in case of a poor response to PDE5i treatment.	2	A
Consider testosterone therapy in hypogonadal men with diabetes.	2	B

5.5 Recommendations for testosterone replacement therapy

Recommendations	LE	GR
Fully inform the patient about expected benefits and side-effects of the treatment option. Select the preparation with a joint decision by an informed patient and the physician.	3	A
Use short-acting preparations rather than long-acting depot administration when starting the initial treatment, so that therapy can be adjusted or stopped in case of adverse side-effects.	3	B
Do not use testosterone therapy in patients with male infertility and active child wish since it may suppress spermatogenensis.	1b	A
Only use human chorionic gonadotropin treatment for hypogonadotrophic hypogonadal patients with simultaneous fertility treatment.	1b	B
In patients with adult-onset hypogonadism, only prescribe testosterone treatment in men with multiple symptoms and if weight loss, lifestyle modification and good treatment balance of comorbidities have proven unsuccessful.	2	A

Recommendations	LE	GR
Perform haematological, cardiovascular, breast and prostatic assessment before the start of treatment.	1a	A
Monitor testosterone, haematocrit, haemoglobin and prostate-specific antigen (PSA) during testosterone treatment.	3	A
Offer testosterone treatment cautiously in symptomatic hypogonadal men who have been surgically treated for localised prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis): treatment should be restricted to those patients with a low risk for recurrent prostate cancer (i.e. Gleason score < 8; pathological stage pT1-2; pre-operative PSA < 10 ng/mL) and should not start before one year of follow-up.	3	B
Assess for cardiovascular risk factors before commencing testosterone treatment and optimise secondary prevention in men with pre-existing cardiovascular disease.	1a	A
Treat men with hypogonadism and either pre-existing cardiovascular disease, venous thromboembolism or chronic cardiac failure who require testosterone treatment with caution by monitoring carefully with clinical assessment, haematocrit (not exceeding 0.54) and testosterone levels maintained as best possible for age within the mid-normal healthy range.	1b	A

6.7 Recommendations for follow-up

Recommendations	LE	GR
Assess the response to testosterone treatment at three, six and twelve months after the onset of treatment, and thereafter annually.	4	C
Monitor testosterone, haematocrit at three, six and twelve months and thereafter annually. Decrease the testosterone dosage or switch testosterone preparation from parenteral to topical or venesection, if haematocrit is above 0.54. If haematocrit remains elevated, stop testosterone and reintroduce at a lower dose once haematocrit has normalised.	4	C
Assess prostate health by digital rectal examination and prostate-specific antigen (PSA) before the start of testosterone replacement therapy (TRT). Follow-up by PSA tests at three, six and twelve months and thereafter annually.	4	C
Assess men with cardiovascular diseases for cardiovascular symptoms before testosterone treatment is initiated and continue close clinical assessment during treatment.	1b	A