PRISM

POSTGRADUATE INTERNATIONAL SCHOOL OF MEN'S HEALTH

Advisory Board Meeting

In Chicago

PRISM Highlight

20th June 2014

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1. Meeting Objectives

The 2014 PRISM Advisory Board Chicago Meeting was organized by PRISM in Sheraton Chicago Hotel & Towers in 20th June 2014. The PRISM stands for the “Postgraduate International School of Men's Health, a new initia-tive to bring to-gether academicians, medical professionals, health profes-sionals and patients with as major aim to provide a better information about men’s health.

Although in the last two decades a lot of information has been given about women’s health, mainly focused on the menopause and the hor-mone replacement therapy (HRT) , for one reason or anoth-er talking about men’s health was deemed less relevant or interesting. For this rea-son some key opinion leaders in the androgen (male hormone) and uro-logical field started the initiative of PRISM.

The purpose of this meeting was indeed to bring excellent scientists who can discuss about different topics that came up in the last couple of months. The fields of men's health has been very confusing and contro-versial. “If it is confusing for experts, it's even more confusing for practi-tioners and for patients”, a remark during welcoming speech by Dr Jean-Paul Deslypere. Many experts in this field do not agree on andropause if there is a hypogonadism condition, or do not know exactly what are the lower limits of normal testosterone level, or should we give male hor-mones to patients, at risk at prostate cancer or to elderly men or just letting them die by myocardial infarction. So there are so many questions marks which have come up in the last few months and for this reason Be-sins Health Care initiated this meeting to bring all experts together to have informal discussion.

2. OVERVIEW OF ATTENDEES

Advisory Board Faculty

Sandeep Dhindsa, (Odessa, TX)

Mathis Grossman, (Australia)

Michael Zitzmann, (Germany)

Aleksey Zilov, (Russia)

Glenn Cunningham, (Houston, TX)

Marco Marcelli, (Houston, TX)

Abraham Morgentaler, (Boston, MA)

Adriane Dobs, (Baltimore, MD)

Roman Rozhivanov, (Russia) Hugh Jones (UK)

Stephanie Page (Seattle, WA)

Joel Finklestein, (Boston, MA)

David Handelsman, (Australia)

Corporate Attendees

Leo Kokovin

Paul Piette

Jean-Paul Deslypere

Jay Korn Anong

Tom MacAllister

Raymond Zhao

Paul Tobolov

Roland Van der hoop

Luke Horton

Amy Undeejav

Devon Tirpack

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5. About the Speakers

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5. About the Speakers

The 2014 PRISM Advisory Board Chicago Meeting list of speakers in the order of presentation is shown below:

1. **Dr. Sandeep Dhindsa** Associate Professor of Medicine, Texas Tech University Health Sciences Center

2. **Dr. Mathis Grossmann MD., PhD, FRACP** Associate Professor Head of Andrology University of Melbourne Austin Health

3. **Dr. Michael Zitzmann MD.,PhD** Andrologist, Endocrinologist, Diabetologist Sexual Medicine (FECSM) Clinical Andrology / Centre for Reproductive Medicine and Andrology University Clinics Muenster Germany

4. **Dr. T. Hugh Jones M.D.** Centre for Diabetes & Endocrinology, Barnsley Hospital NHS Foundation Trust & Academic Unit of Diabetes Endocrinology & Metabolism, University of Sheffield

5. **Dr. Morgentaler MD., FACS** Founder, Men's Health Boston Associate Clinical Professor of Urology Beth Israel Deaconess Medical Center Harvard Medical School

6. **Dr. Glenn R Cunningham MD., PhD** Professor of Medicine Molecular and Cellular Biology Baylor College of Medicine St. Luke's-BaylorDiabetes Program Houston, Texas

7. **Dr. Adrian Dobs M.D., M.H.S.** Professor of Medicine and Oncology The Johns Hopkins University School of Medicine

8. **Dr. Rozhivanov Roman MD., PhD** National Research Center for Endocrinology, Moscow, Russia

9. **Dr. Marco Marcelli M.D.** Michael E. DeBakey VA Medical Center Baylor College of Medicine Houston, TX 77030

10. **Dr. Joel S. Finkelstein, M.D.** Endocrine Unit Massachusetts General Hospital Associate Professor of Medicine Harvard Medical School

11. **Dr. Stephanie T. Page MD., PhD** Associate Professor of MedicineDepartment of Medicine University of Washington Seattle, WA

12. **Dr. Aleksey Zilov MD., PhD**

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PRISM Advisory Board Meeting Chicago 20th June 2014

Morning Session

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Dr. Sandeep Dhindsa

Associate Professor of Medicine Division of Endocrinology and Metabolism

Texas Tech University Health Sciences Center

Testosterone and estradiol in type 2 diabetes, obesity and the metabolic syndrome

Dr. Dhindsa Presentation Overview:

The topic of presentation of Dr. Dhindsa was "Testosterone and estradiol in Type 2 Diabetes, obesity and the metabolic syndrome". His observation goes back to 10 years ago when he ob-served that many of his patients with type 2 diabetes show low level of blood testosterone. Dr. Dhindsa's research in 2004 on 103 male patients with T2D showed that 33% had low blood free testosterone (FT) and 44% low total testosterone (TT) level (Dhindsa, Prabhakar et al. 2004).

Later his research in this field indicated a clear trend and correlation between the patients weight and BMI and the level of free testosterone. The effect of having diabetes on the free testosterone concentration was similar to that of an increase in BMI of 6 kg/m2 in a man without diabetes or similar to that of a 5 year increase in age (Dhindsa, Miller et al. 2010).

Therefore, there seems to be a relationship between free testosterone levels in men with sex-ual dysfunction and number of metabolic syndrome components and also insulin sensitivity in Type 2 Diabetes (Corona, Mannucci et al. 2006).

Frequent Occurrence of Hypogonadotrophic Hypogonadism in Type 2 Diabetes

- 103 consecutive, type 2 diabetic male patients
- Total T (TT), free T by equilibrium dialysis (FT), calculated FT (cFT), and calculated bioavailable T levels (BT) were determined
- Mean age was 54.7 ± 1.1 years (range, 28-80)
- Mean BMI was 33.4 ± 0.8 kg/m^2 (range, 17.6-63.1)
- **33% had low free testosterone**
- 43.7% had low TT; 36% had low BT
- LH and FSH significantly lower in the hypogonadal group
- Testosterone concentrations were not related to HbA1c, duration of diabetes, complications of diabetes or use of insulin or statins

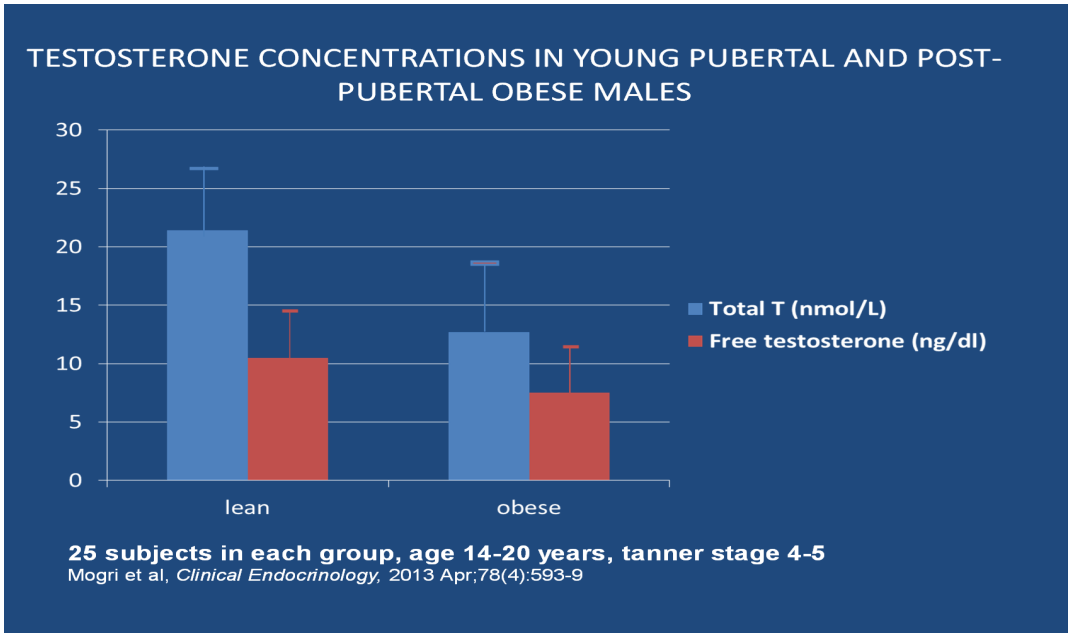
Corona, G., E. Mannucci, C. Schulman, L. Petrone, R. Mansani, A. Cilotti, G. Balercia, V. Chiarini, G. Forti and M. Mag-gi (2006). "Psychobiologic correlates of the metabolic syndrome and associated sexual dysfunction." Eur Urol 50(3): 595-604; discussion 604.

Dhindsa, S., M. G. Miller, C. L. McWhirter, D. E. Mager, H. Ghanim, A. Chaudhuri and P. Dandona (2010). "Testosterone concentrations in diabetic and nondiabetic obese men." Diabetes Care 33(6): 1186-1192.

Dhindsa, S., S. Prabhakar, M. Sethi, A. Bandyopadhyay, A. Chaudhuri and P. Dandona (2004). "Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes." J Clin Endocrinol Metab 89(11): 5462-5468.

Dr. Dhindsa demonstrated data from his clinical study, which compared free testosterone concentrations in type 1 versus type 2 diabetic men between the ages of 18-35 years (Chandel, Dhindsa et al. 2008). The mean BMI of men with type 1 and type 2 diabetes was 27.4 ± 1.2 and 38.6 ± 2 ($p<0.001$) respectively and only men with T2D showed significant lower FT level.

Then he was curious to see the effect of obesity on plasma testosterone concentrations in pubertal and post-pubertal young males (Mogri, Dhindsa et al. 2013). In-terestingly, testosterone concentrations of young obese pubertal and post-pubertal males were 40-50% lower than those with normal BMI. Obesity in young males was associated with low testosterone concentrations, which were not secondary to an increase in estradiol concentrations.



Chandel, A., S. Dhindsa, S. Topiwala, A. Chaudhuri and P. Dandona (2008). "Testosterone concentration in young patients with diabetes" Diabetes Care 31(10): 2013-2017.

Mogri, M., S. Dhindsa, T. Quattrin, H. Ghanim and P. Dandona (2013). "Testosterone concentrations in young pubertal and post-pubertal obese males." Clin Endocrinol (Oxf) 78(4): 593-599.

Endocrinol Metab. 2008 Jul;93(7):2737-45.

In fact, further studies showed a positive relation between FT and Estradiol concentrations in Men with Type 2 Diabetes, which was consistent with the other studies such as European male aging study (Wu, Tajar et al. 2008).

Therefore, hypogonadotropic hypogonadism of type 2 diabetes was not mediated by elevated estradiol concentrations. Further studies at clinical and cellular levels indicated that men with T2D and Hypogonadotropic Hypogonadism (HH) were more insulin resistant than those with nor-mal testosterone and HH is associated with lower expression of mediators of insulin signaling in adipose tissue as compared with eugonadal patients. Following Testosterone replacement the expression of mediators of insulin signaling increased and there was reduction in expression of markers interfering with insulin signaling leading to improved insulin sensitivity.

European Male Aging Study

	Eugonadal	Secondary hypogonadism	Primary hypogonadism	Compensated hypogonadism
n	2436 (76.7%)	375 (11.8%)	63 (2.0%)	303 (9.5%)
Age (yr)	58.5 (10.7)	59.4 (10.4)	70.0 (9.0)	67.3 (9.9)
BMI (kg/m^2)	27.3 (3.8)	30.8 (4.8)	29.0 (3.9)	26.8 (3.6)
Total T (nmol/liter)	17.8 (5.3)	8.7 (1.6)	7.5 (2.5)	18.3 (5.6)
Free T (pmol/liter)	314.7 (77.5)	194.4 (45.6)	138.7 (59.8)	265.1 (81.4)
LH (U/liter)	5.2 (1.8)	4.4 (1.9)	18.0 (10.3)	14.1 (6.5)
SHBG (nmol/liter)	43.2 (17.9)	26.5 (12.3)	40.1 (18.5)	60.1 (25.2)
E2 (pmol/liter)	75.9 (24.0)	57.2 (17.8)	54.8 (25.4)	84.9 (29.3)

Wu FC1, Tajar A, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva F, Forti G, Giwercman A, Huhtaniemi IT, Kula K, Punab M, Boonen S, Vanderschueren D; European Male Aging Study Group. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin

In conclusion, hypogonadotropic hypogonadism is frequent in type 2 diabetes (33%) and hy-pogonadism is not associated with type 1 diabetes. Obesity and metabolic syndrome are associ-ated with hypogonadism (20-25%). Hypogonadotropic hypogonadism of type 2 diabetes is not mediated by elevated estradiol concentrations and men with T2D and HH are more insulin re-sistant than those with normal T based on HE clamps. HH is associated lower expression of medi-ators of insulin signaling in adipose tissue as compared with eugonadal patients. Following Tes-tosterone replacement the expression of mediators of insulin signaling increases and there is re-duction in expression of markers interfering with insulin signaling leading to improved insulin sensitivity.

CONCLUSIONS

1) men with T2D and HH are more insulin resistant than those with normal T based on HE clamps;
2) HH is associated lower expression of mediators of insulin signaling in adipose tissue as compared with eugonadal patients
3) Following Testosterone replacement the expression of mediators of insulin signaling increases and there is reduction in expression of markers interfering with insulin signaling leading to improved insulin sensitivity

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Dr. Mathis Grossmann

Associate Professor of Head of Andrology

University of Melbourne Austin Health

Testosterone Treatment in Men with Type 2 Diabetes

Dr. Grossmann Presentation Overview:

The topic of presentation of Dr. Grossmann was "Testosterone Treatment in Men with Type 2 Diabetes". In introduction section, Dr Grossmann addressed the "Magnitude of the problem". He mentioned that "The Endocrine Society Clinical Practice Guide-line" published in 2010 indicat-ed that the information about the benefits and risks of testosterone therapy in men with type 2 diabetes is either limited or not available (Bhasin, Cunningham et al. 2010). Similarly, The Interna-tional Society of Andrology publication in 2009 suggested that recommendation of testosterone therapy for the metabolic syndrome or diabetes is prema-ture based on current available infor-mation (diabetes 2014).

The 2014 publication of American Diabetes Association Standards of medical care in diabetes also suggested that the evidence for effects of testosterone replacement in diabetes on outcomes was mixed and not clear (Wang, Nieschlag et al. 2009). The problem with all these guidelines is first quality of evidences.

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM; Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 95:2536-2559,2010.

American Diabetes Association, Standards of medical care in diabetes, Diabetes Care. 2014 Jan;37 Suppl 1:S14-80, 2014.

Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, Morley JE, Schulman C, Thompson IM, Weidner W, Wu FC; Investigation, treatment, and monitoring of late-onset hy-pogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. J An-drol 30:1-9, 2009

The next question Dr Grossmann addressed was the magnitude of the issue of hy-pogonadism in men with type 2 diabetes. This was not a straight forward question to answer because of the absence of clinical gold standard diagnosis for hypogonadism.

The Cross-sectional study of 355 middle-aged obese men with T2D (Kapoor, Aldred et al. 2007), showed that about 55-75% had clearly low level of testosterone and clinical symptoms compatible with androgen deficiency. However, the symptoms of hy-pogonadism consistent with androgen deficiency were non-specific and correlated more strongly with age than with the testosterone levels. Also another study in 329 patients (115 T2D) indicated weak relationship of testosterone levels with symptoms (Biswas, Hampton et al. 2012).

Kapoor D1, Aldred H, Clark S, Channer KS, Jones TH.; Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes Care 30:911-7, 2007.

Biswas M, Hampton D, Newcombe RG, Rees DA.; Total and free testosterone concentrations are strongly influenced by age and central obesity in men with type 1 and type 2 diabetes but correlate weakly with symptoms of androgen deficiency and diabetes-related quality of life. Clin Endocrinol (Oxf) 76:665-73, 2012.

The next question Dr Grossmann addressed was about the prevalence of low testosterone level is in men with type 2 diabetes. Looking at past published studies, the level of free and total testos-terone ranged from 36 to 57 percent but the mean level was modestly reduced relative to refer-ence ranges in healthy young men (Dhindsa, Prabhakar et al. 2004, Kapoor, Aldred et al. 2007, Grossmann, Thomas et al. 2008).

Prevalence of Low Testosterone in Men with Type 2 Diabetes

	N	Age (years)	BMI (kg/m²)	HbA1c (%)	Total T (nmol/L) (ng/dl)	% Low Total T*	% Low Free T*
Grossmann[1]	580	65	30.1	7.5	10.5 302	43% (<10 nmol/L)	57% (<230 pmol/L)
Kapoor[2]	355	58	32.2	7.2	12.7 365	51% (<12 nmol/L)	50% (<255 pmol/L)
Dhinsdsa[3]	103	55	33.4	8.4	12.2 360	44% (<10.4 nmol/L)	36% (<225 pmol/L)

Values are means

5% Total T ≤5.2 nmol/L (150 ng/dl)[1]

*Relative to reference ranges based on healthy young men

ng/dl = nmol/L x 28.8

[1]JCEM 93:1834, 2008; [2]Diabetes Care 30:1911, 2007; [3]JCEM 89:5462, 2004

In next section, Dr Grossmann provided an overview of the Pathogenesis and therapeutic implica-tions of testosterone treatment in men with Type 2 Diabetes and then provided an overview of the randomized clinical trials (RCTs) of testosterone treatment in men with Type 2 Diabetes. In ten RCTS in men not selected for abnormal glucose metabolism, the effects of testosterone thera-py on insulin resistant was seen in only 2 trails, while 8 trials found no effect.

Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, Macisaac RJ, Clarke S, Zajac JD, Jerums G.; Low testosterone lev-els are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab 93:1834-1840, 2008.

Kapoor D, Aldred H, Clark S, Channer KS, Jones TH.; Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes Care 30:911-7, 2007.

Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P; Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 89:5462-8, 2004.

In men with type 2 diabetes mellitus, his randomized controlled trial study evaluated the effect of testosterone treatment on insulin resistance (HOMA-IR) and other secondary outcomes. The testosterone therapy did not improve insulin resistance for HOMA-IR compared with placebo or glycemic control, despite a decrease in fat mass and an increase in lean mass.

Testosterone therapy reduced subcutaneous but not vis-ceral abdominal adipose tissue. In another study, testosterone treat-ment did not im-prove constitutional and sexual symptoms monitored by AMS (Aging Men Symptom Score), IIEFF-5 (International Index of Erectile Function-5) in men with T2D. Other RCTs also indicated testosterone therapy cased metaboli-cally favourable changes in body composition and modest improvements in insulin resistance.

In conclusion, men with T2D/metabolic syndrome commonly present with non-specific symptoms and modestly low testos-terone levels and low testosterone identifies an ad-verse metabolic phenotype. Testosterone increases with weight loss, sug-gesting that the HPT axis suppression is functional. RCTs of testosterone therapy have shown meta-bolically favorable chang-es in body composition and modest improvements in insulin resistance.

Conclusions

1. Men with T2D/ MetS commonly present with non-specific symptoms and modestly low testosterone
2. Low testosterone identifies an adverse metabolic phenotype
3. Testosterone increases with weight loss, suggesting that the HPT axis suppression is functional
4. RCTs of testosterone therapy have shown metabolically favourable changes in body composition and modest improvements in insulin resistance
5. **Further clinical trials should target men with:**
   -lower baseline T levels/ higher baseline HbA1c
   -pre-/ recent onset diabetes
   -longer duration
   -exclude older men with pre-existing heart disease
   -compare to lifestyle program rather than placebo

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Dr. Michael Zitzmann

Andrologist, Endocrinologist, Diabetologist

Sexual Medicine (FECSM)

University Clinics Muenster Germany

Testosterone deficiency, insulin resistance and the metabolic syndrome

Dr. Zitzmann Presentation Overview:

The topic of presentation of Dr. Zitzmann was “Testosterone deficiency, insulin resistance and the metabolic syndrome”. In the introduction section, Dr. Zitzmann mentioned about a new Eu-ropean guideline (2012) for testosterone deficiency based on observations from large clinical tri-als on more than 10,000 patients. The guideline defined the threshold level of total testosterone at 12.1 nmol/L or free testosterone at 243 pmol/L for indications of testosterone therapy for hy-pogonadism considering clinical symptoms such as loss of libido, depressive mood, and metabolic disorders. Also, the European Male Aging Study (EMAS) on 3174 subjects aged 40-79 year old showed clear correlation between testosterone level and BMI (Wu, Tajar et al. 2008). The study of prevalence of hypogonadism in 1687 men presenting to an outpatient unit showed an associa-tion between age and prevalence of hypogonadism in healthy-moderately obese subjects (BMI < 25 - 29 kg/m2), while no significant correlation observed in patients who were obese (BMI ≥ 30 kg/m2) (Corona, Rastrelli et al. 2011).

Wu, F. C., A. Tajar, S. R. Pye, A. J. Silman, J. D. Finn, T. W. O'Neill, G. Bartfai, F. Casanueva, G. Forti, A. Giwercman, I. T. Huhtaniemi, K. Kula, M. Punab, S. Boonen and D. Vanderschueren (2008). "Hypothalamic-pituitary-testicular axis disrup-tions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study." J Clin En-docrinol Metab 93(7): 2737-2745.

Corona, G., G. Rastrelli, M. Monami, C. Melani, D. Balzi, A. Sforza, G. Forti, E. Mannucci and M. Maggi (2011). "Body mass index regulates hypogonadism-associated CV risk: results from a cohort of subjects with erectile dysfunction." J Sex Med 8(7): 2098-2105.

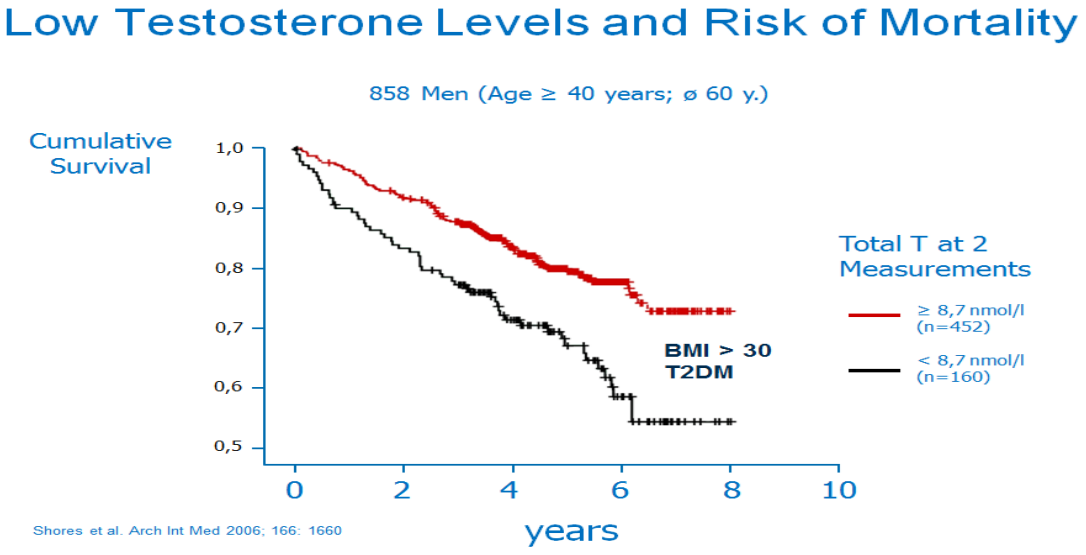
The IDF publication in 2007 estimated that some 246 million people, or 5.9%, in the age group 20-79 had diabetes worldwide and more than 70% of these live in the developing countries (IDF diabetes atlas 2007). The worldwide estimate is expected to increase to some 380 million, or 7.1% of the adult population, by 2025. The largest increases will take place in the regions dominated by developing economies. Previous study in 2162 patients revealed that the crude prevalence rate of hypogonadism was 38.7% (Mulligan, Frick et al. 2006). The odds ratios for having hypogonadism were significantly higher in men with hypertension (1.84), hyperlipidemia (1.47), diabetes (2.09), obesity (2.38), prostate disease (1.29) and asthma or chronic obstructive pulmonary disease (1.40) than in men without these conditions.

Risk factor	Hypogonadism prevalence rate (95% CI)	Odds ratio (95% CI)
Obesity	52.4 (47.9–56.9)	2.38 (1.93–2.93)
Diabetes mellitus	**50.0 (45.5–54.5)**	**2.09 (1.70–2.58)**
Hypertension	42.4 (39.6–45.2)	1.84 (1.53–2.22)
Hyperlipidemia	40.4 (37.6–43.3)	1.47 (1.23–1.76)

In the next section, Dr. Zitzmann provided an overview of the published criteria for the definition of the metabolic syndrome. A new criteria was developed based on the out-come of meeting between several major organizations in an attempt to unify criteria in 2009 (Alberti, Eckel et al. 2009). The five criteria were defined as Waist Circumference > 94-102 cm, Triglycerides > 150 mg/dl, HDL-Cholesterol < 40 mg/dl, Arterial Blood Pres-sure > 130 mmHg systolic and/or > 85 mmHg diastolic, and Fasting glucose > 100 mg/dl or known Type 2 Diabetes mellitus. Three abnormal findings out of 5 could qualify a per-son for the metabolic syndrome.

Mulligan, T., M. F. Frick, Q. C. Zuraw, A. Stemhagen and C. McWhirter (2006). "Prevalence of hypogonadism in males aged at least 45 years: the HIM study." Int J Clin Pract 60(7): 762-769.

In next section, Dr. Zitzmann provided a review on underlying mechanism of hypogonadism in rela-tion to metabolic disorders. One suggested mechanism was that visceral fat leads to increase insulin, leptin, and Interleukin 6 levels, which subsequently lowers tes-tosterone level. Another mechanism is that visceral fat increases angiotensinogen, which adds to the effects of leptin and inflamma-tory cy-tokines and leads to metabolic syndrome. The results from the European Male Ageing Study on 2395 subjects also indicated that patients who lost 15% of their weights, regained total testosterone level without any treatment while patients who gained more than 15% body weight, showed significant decreased in total testosterone level (Camacho, Huhtaniemi et al. 2013).



In the last part of his presentation, Dr Zitzmann reviewed testosterone replacement therapy studies including his work on the time-dependent and symptom-specific onset of effects of testosterone sub-stitution (Saad, Aversa et al. 2011).

Camacho, E. M., I. T. Huhtaniemi, T. W. O'Neill, J. D. Finn, S. R. Pye, D. M. Lee, A. Tajar, G. Bartfai, S. Boonen, F. F. Casanueva, G. Forti, A. Giwercman, T. S. Han, K. Kula, B. Keevil, M. E. Lean, N. Pendleton, M. Punab, D. Vanderschueren and F. C. Wu (2013). "Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study." Eur J Endocrinol 168(3): 445-455.

Saad, F., A. Aversa, A. M. Isidori, L. Zafalon, M. Zitzmann and L. Gooren (2011). "Onset of effects of testosterone treat-ment and time span until maximum effects are achieved." Eur J Endocrinol 165(5): 675-685.

In conclusion, Dr Zitzmann suggested to encourage patients to adopt to a healthy life style (lack of physical activity, overnutrition, smoking, and stress) in first place. Then since recent stydies indicated that low testosterone levels predicted an increase in all-cause mortality during long-term follow-up and testosterone replacement improved survival in hypogonadal men with type 2 diabetes (Muraleedharan, Marsh et al. 2013), it is recommended to consider adequate testosterone replacement therapy to increase the survival rate and offer happy life for patients.

Muraleedharan, V., H. Marsh, D. Kapoor, K. S. Channer and T. H. Jones (2013). "Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes." Eur J Endocrinol 169(6): 725-733.

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Dr. Thomas Hugh Jones

Centre for Diabetes & Endocrinology Barnsley Hospital, NHS Foundation Trust & Academic Unit of Diabetes, Endocrinology & Metabolism, University of Sheffeild

Does TRT Decrease CV Risk?

Dr. Jones Presentation Overview:

The topic of presentation of Dr. Jones was "Does TRT Decrease CV Risk?" In introductory session, Dr Jones provided an overview of Cardiovascular Disease (CVD) healthspan and lifespan. Patients with CVD have certain risk factors, which leads to symptoms such as erectile dysfunction (ED), angina, breathless, and fatigue. These leads to physical, psychological, and sexual health issues, many of them are affecting men's quality of life (QOL). He looked at ED, which is one of the main reason patients refer to his clinic and its impact on QOL of 355 men with T2D. All subjects com-pleted SF-36 health and Androgen Deficiency of the Aging Male questionnaires along with meas-urement of testosterone levels. A subgroup of 126 ED patients completed the International Index of Erectile Function-5 (IIEF-5) questionnaire (Brooke, Walter et al. 2014).

Patients who reported having ED had an average SF-36 score of 9.1% less than those without ED ($p < 0.001$). Lower testosterone and greater severity of ED independently correlated with poorer physical function, so-cial function, vitality and decline in general health domains of the SF-36. This was the first study to report that testosterone deficiency and severity of ED were both independently associated with reduced QOL in men with T2D.

Brooke, J. C., D. J. Walter, D. Kapoor, H. Marsh, V. Muraleedharan and T. H. Jones (2014). "Testosterone deficiency and severity of erectile dysfunction are independently associated with reduced quality of life in men with type 2 diabetes." Andrology 2(2): 205-211.

In the next section, Dr. Jones discussed the relationship between testosterone level and mortali-ty. Several large population clinical trials evaluated the effect of testosterone on all-cause mortal-ity in disease specific populations. Majority of these studies showed that low testosterone is a biomarker for prediction of mortality risks, especially in patients with T2D and CVD. In his follow up study of 930 consecutive men with coronary disease, Dr Jones found that testosterone defi-ciency was common and impacted significantly negatively the survival (Malkin, Pugh et al. 2010). He also studies testosterone deficiency and mortality in 581 men with type 2 diabetes and mor-tality was increased in the low testosterone group (17.2%) compared with the normal testos-terone group (9%; P=0.003) when controlled for covariates. Testosterone replacement therapy was associated with a reduced mortality of 8.4% compared with 19.2% (P=0.002) in the untreat-ed group (n=174). Therefore, low testosterone levels predict an increase in all-cause mortality during long-term follow-up and testosterone replacement may improve survival in hypogonadal men with type 2 diabetes (Muraleedharan, Marsh et al. 2013).

EDITOR'S CHOICE

PRESS RELEASE

Low serum testosterone and increased mortality in men with coronary heart disease

Chris J Malkin,[1] Peter J Pugh,[1] Paul D Morris,[1] Sonia Asif,[1] T Hugh Jones,[2,3] Kevin S Channer[1]

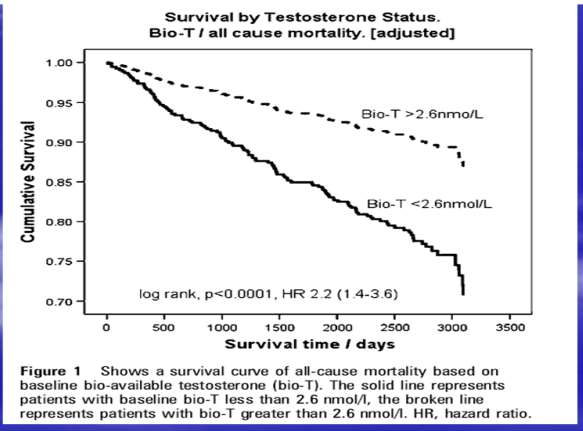


Figure 1 Shows a survival curve of all-cause mortality based on baseline bio-available testosterone (bio-T). The solid line represents patients with baseline bio-T less than 2.6 nmol/l, the broken line represents patients with bio-T greater than 2.6 nmol/l. HR, hazard ratio.

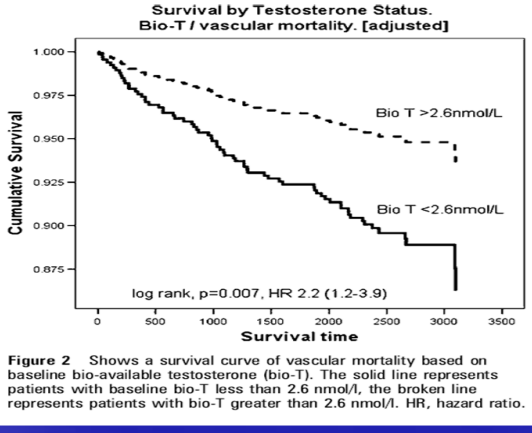


Figure 2 Shows a survival curve of vascular mortality based on baseline bio-available testosterone (bio-T). The solid line represents patients with baseline bio-T less than 2.6 nmol/l, the broken line represents patients with bio-T greater than 2.6 nmol/l. HR, hazard ratio.

N=930

Malkin CJ et al. Heart 2010;96:1821-25

Malkin, C. J., P. J. Pugh, P. D. Morris, S. Asif, T. H. Jones and K. S. Channer (2010). "Low serum testosterone and increased mortality in men with coronary heart disease." Heart 96(22): 1821-1825.

Muraleedharan, V., H. Marsh, D. Kapoor, K. S. Channer and T. H. Jones (2013). "Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes." Eur J Endocrinol 169(6): 725-733.

Dr Jones described in next part of his presentation the macrovascular disease and diagnosis in Type 2 diabetes, which is widespread as 75% of all deaths in people with Type 2 diabetes are due to cardiovascular disease. Complications start early in the development of Type 2 diabetes and may be present at diagnosis. Increasing blood glucose levels were associated with an increased risk of several debilitating microvascular complications.

Studies have shown that the risk of cardiovascular disease raised with increasing blood glucose levels. Several Epidemiological extrapolations from this study showed that a 1% higher HbA1c was associated with a highly significant (p<0.0001) 21% increase in risk of diabetes-related deaths, 14% increase in myocardial infarction, and 43% increase in peripheral vascular disease. Other studies showed correlation between bioavailable testosterone and waist circumference in men with Type 2 diabetes (Kapoor, Aldred et al. 2007). Effect of weight loss on testosterone lev-els as discussed by Dr Grossman is clear and we encourage our patients to lose weight (Grossmann 2011).

Kapoor, D., H. Aldred, S. Clark, K. S. Channer and T. H. Jones (2007). "Clinical and biochemical assessment of hypogonad-ism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity." Diabetes Care 30(4): 911-917.

Grossmann, M. (2011). "Low testosterone in men with type 2 diabetes: significance and treatment." J Clin Endocrinol Metab 96(8): 2341-2353.

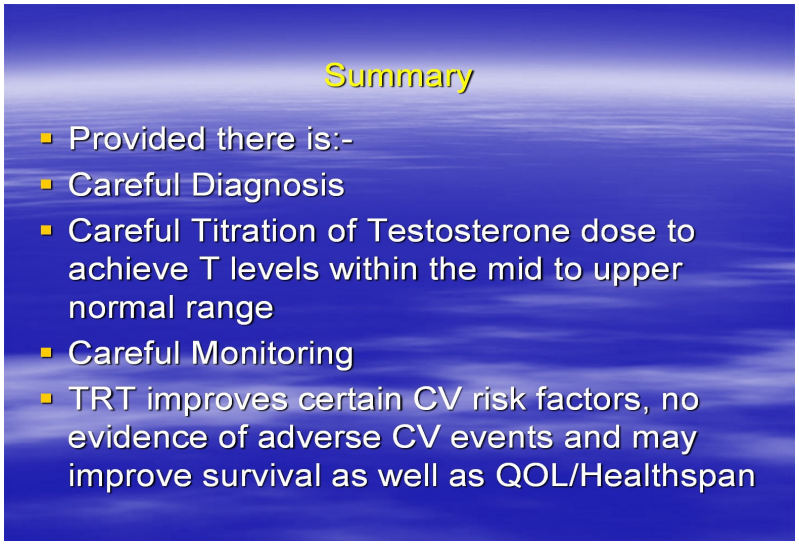
In last section, Dr Jones reviewed the testosterone replacement therapy and its impact on CVD. In the study that transdermal testosterone replacement therapy was used over a 6-month peri-od, there was associated beneficial effects on insulin re-sistance, total and LDL-cholesterol, Lpa, and sexual health in hypogonadal men with type 2 diabetes and/or metabolic syn-drome (Jones, Arver et al. 2011). In a randomized, double-blind, placebo-controlled study, low-dose transder-mal testosterone therapy improved angina threshold in men with chronic stable angina (English, Steeds et al. 2000). Dr Jones presented pub-lished evidences of the effects of endogenous and therapeutic testosterone on the heart and the human cardiovascular system with an emphasis on the pathologic syndrome of chronic heart failure. The TIMES2-Study by Jones et al also showed that over a 6-month period, transdermal testosterone replacement therapy was associ-ated with beneficial effects on insulin resistance, total and LDL-cholesterol, Lpa, and sexual health in hypogonadal men with type 2 diabetes and/or Metabolic syndrome (Jones, Arver et al. 2011). The effect of TRT in poorly controlled T2D (n=104) showed no changes in hypoglycaemic medications in first 3 months and some reduction on total cholesterol without or with statins

Jones, T. H., S. Arver, H. M. Behre, J. Buvat, E. Meuleman, I. Moncada, A. M. Morales, M. Volterrani, A. Yellowlees, J. D. Howell and K. S. Channer (2011). "Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study)." Diabetes Care 34(4): 828-837.

English, K. M., R. P. Steeds, T. H. Jones, M. J. Diver and K. S. Channer (2000). "Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study." Circulation 102(16): 1906-1911.

In conclusion, Dr Jones's recommendation was that provided careful diagnosis and ti-tration of testosterone dose to achieve levels within the mid to upper normal range, TRT improves certain CV risk factors.

There is no evidence of adverse CV events and TRT may improve survival as well as QOL/Healthspan.



PRISM

POSTGRADUATE INTERNATIONAL SCHOOL OF MEN`S HEALTH

Dr Abraham Morgentaler

Founder Men's Health Boston

Associate Clinical Professor of Urology

Harvard Medical School

Testosterone Therapy and Cardiovascular Risk

Dr. Morgentaler Presentation Overview:

The topic of presentation of Dr. Morgentaler was Testosterone Therapy and Cardiovascular Risk". In introductory session, Dr Morgentaler provided an overview of overselling testosterone dan-gerously. He mentioned lots of our attitude toward testosterone is either philosophical or opin-ion. It took 70 years to discover that testosterone therapy was not dangerous for prostate cancer and suddenly, new concern emerged regarding CV risk of testosterone therapy. It all started with the first article published in JAMA in Nov 2013 (Vigen, O'Donnell et al. 2013) entitled "Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels". Lot of headlines around the world broadcasted the article findings that the use of testosterone therapy was associated with increased risk of adverse CV outcomes. This was followed by second publication in January 2014, entitled "Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men (Finkle, Greenland et al. 2014). Within a couple of days, FDA announced that is going to review the safety issues and CV risk of using testosterone.

Finkle, W. D., S. Greenland, G. K. Ridgeway, J. L. Adams, M. A. Frasco, M. B. Cook, J. F. Fraumeni, Jr. and R. N. Hoover (2014). "Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men." PLoS One 9(1): e85805.

Vigen, R., et al., Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. Jama, 2013. 310(17): p. 1829-36.

This was a big deal and at least in United States, this became a major health story. New York Times published an editorial opinion pages entitled “Overselling Testosterone, Dangerously”, with the comments that men who get testosterone prescription embark-ing on a dangerous journey. As a result, we have now in United States television ads from lawyers who are look-ing for men who had heart attack after starting testosterone. The impact of these two articles was remarkable and changed medical practice. Pa-tients who were on testosterone therapy for a while and doing well, stopped treatment because of thinking will get heart attack. We have patients who should be on testosterone therapy but refuse to take medication and we have physicians who stopped offering testosterone therapy all together. This altered scien-tific concepts and created a brand-new area of medical malpractice. One would hope that such precipitous changes would be based on prospective, controlled trials that showed indis-putable evi-dence of CV risks with testosterone therapy, which was not the case and all incorrect.

In the next section, Dr. Morgentaler explained details of evidences and their original sources. Be-fore the JAMA article, two anti-Pharma expert in botanical medicine, Nicole Dubowitz and Dr. Adriane Fugh-Berman, published Outside Opinion article in Chicago Tribune Sept 15, 2013, enti-tled “Testosterone Treatments Are Dangerous For Men”. They claimed that “Testosterone drugs are associated with more heart attacks, blood clots and anaemia, worsening heart failure, and increased prostate cancer risk”, which are all false. Why do we believe things that obviously aren’t true? Dr. Morgentaler answered that question by saying that people will believe anything if a person says, ‘Scientists have discovered that”.

Dr. Morgentaler then reviewed evidences published by Finkle et al article (Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men) and then re-viewed the evidences of published article by Vigen et al in JAMA in 2013 entitled “Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testos-terone levels” (Vigen, O'Donnell et al. 2013). Dr. Morgentaler also reviewed the evidences of published article by Xu et al (Xu, Freeman et al. 2013) entitled “Testosterone therapy and cardio-vascular events among men: a systematic review and meta-analysis of placebo-controlled ran-domized trials”.

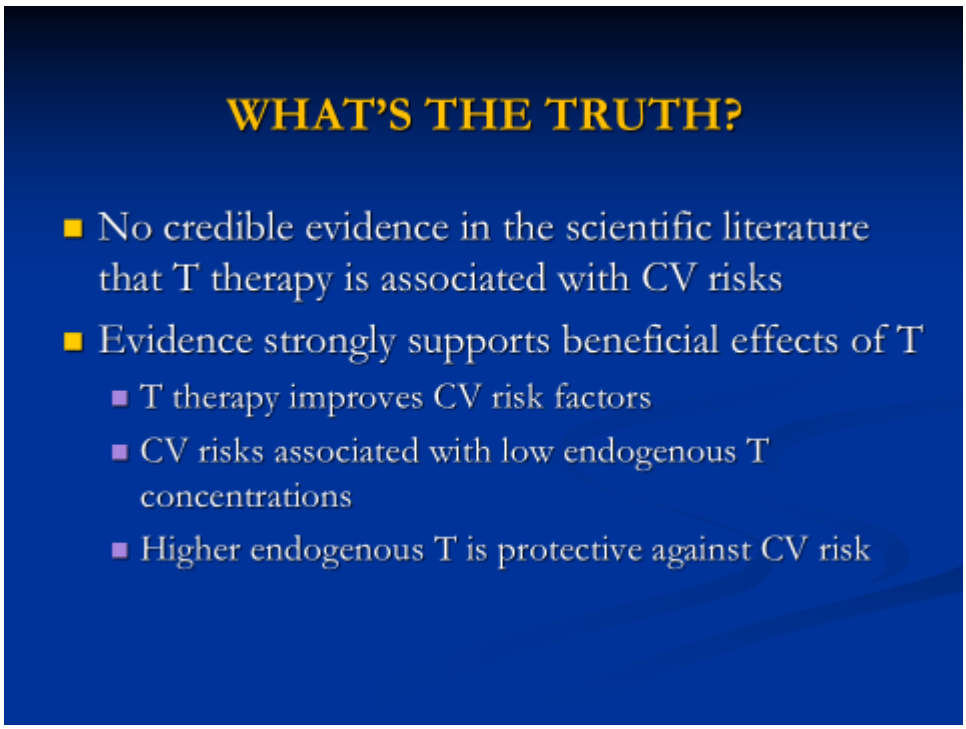
Finkle, W. D., S. Greenland, G. K. Ridgeway, J. L. Adams, M. A. Frasco, M. B. Cook, J. F. Fraumeni, Jr. and R. N. Hoover (2014). "Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men." PLoS One 9(1): e85805.

Vigen, R., et al., Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. Jama, 2013. 310(17): p. 1829-36.

Xu, L., G. Freeman, B. J. Cowling and C. M. Schooling (2013). "Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials." BMC Med 11: 108.

In the last part of his presentation, Dr Morgentaler mentioned about the efforts of Androgen Study Group, which submitted to FDA on May 7, 2014 the following evidences: Review of lit-erature submitted to FDA, Detailed analysis of studies reporting increased CV risks, and overview of 30 years of literature that has shown beneficial effects of higher endogenous testosterone or testosterone therapy (Compilation of 3 appendices, 8 tables).

In conclusion, there were 46 studies that reported beneficial effects with zero study to report any harmful effect of higher testosterone (Endogenous or Treated). Therefore, no credible evidence in the scientific literature exists to support that testosterone therapy is associated with CV risks and all evidences strongly support beneficial effects of testosterone to improve CV risk factors. The assertion of risk without solid evidence is irresponsible and such claims of increased CV risk promoted by those who were not involved in the care of men with testosterone deficiency such as anti-pharma advocates, media, plaintiff attorneys, and anti-sex groups.



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Dr Glenn Cunningham
Professor of Medicine Molecular and Cellular Biology
Baylor College of Medicine
St.Luke's– Baylor Diabetes Program
Houston, Texas

TRT and the Prostate

Dr. Cunningham Presentation Overview:

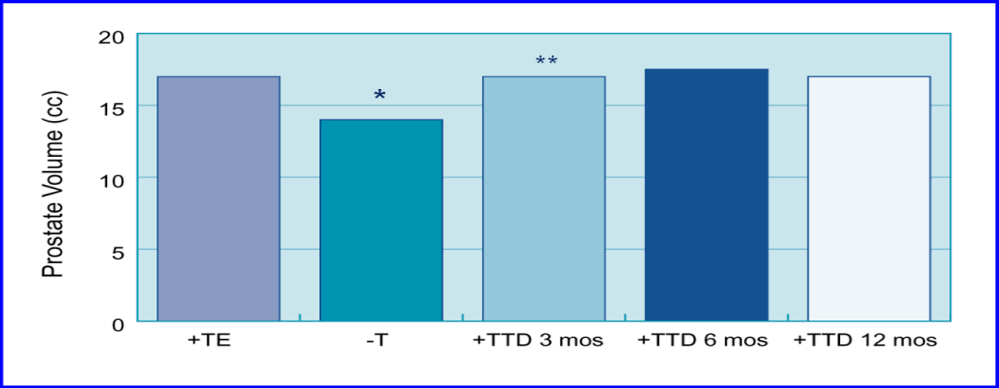
The topic of presentation of Dr. Cunningham was "TRT and the Prostate". In Introduction section, Dr Cunningham mentioned that the hot controversy topic used to be "Testosterone and Prostate cancer" but it seems it has found a hotter topic that is now is "Testosterone and Cardiovascular risks". Speaking of controversy, this was the statement was made by Andrew von Eschenbach, M.D., Director of National Cancer Institute (who has become later the director of FDA) in New York Times (March 11, 2003): Recognizing the dependency of prostate cancer on testosterone, I am not convinced there is enough evidence on the safety of testosterone to justify its widespread use." The prostate is off course an androgen target tissue. The prostate increases in size after the onset of puberty as testosterone levels increase. The prostate does not increase in size in genetic males who have complete androgen insensitivity (Corbetta, Muzza et al. 2011).

Corbetta, S., M. Muzza, L. Avagliano, G. Bulfamante, L. Gaetti, C. Eller-Vainicher, P. Beck-Peccoz and A. Spada (2011). "Gonadal structures in a fetus with complete androgen insensitivity syndrome and persistent Mullerian derivatives: comparison with normal fetal development." Fertil Steril 95(3): 1119.e1119-1114.

Dr Cunningham described in next part of his presentation the potential effects of testosterone replacement therapy on the prostate, including possible increase in prostate volume, increased risk of lower urinary tract system and BPH, increase in PSA levels, and stimulate growth of an occult tumor. Earlier studies published by Snyder showed that testosterone replacement therapy in hypogonadal men led to increased prostate volume and sexual function to the normal healthy level. The full effect of testosterone on bone mineral density took 24 months, but the full effects on the other tissues took only 3-6 months. These results provided the basis for monitoring the magnitude and the time course of the effects of testosterone replacement in hypogonadal men (Snyder, Peachey et al. 2000). The study of Behr et al in 1994 also shows that prostate volume increased by testosterone treatment to a normal healthy range in hypogonadal men (Behre, Bohmeyer et al. 1994). Meikle et al studied mean prostate volumes during treatment with testosterone enanthate or with transdermal patch were comparable. Prostate volume rose significantly ($P<0.001$) after 3 months of transdermal patch therapy compared to prostate volume measured during the washout period without testosterone therapy of any kind (-T). However, mean prostate volume in patients during testosterone transdermal therapy was similar to that seen in eugonadal men. Furthermore, after 3 months of therapy with transdermal testosterone, mean prostate volume remained steady and within the normal range throughout the duration of the study (Meikle, Arver et al. 1997).

Mean Prostate Volume +/- Treatment with Testosterone Enanthate or Transdermal Patch

Meikle AW, et al. *Urol.* 1997;49:191-196.



*P<0.001 decrease, -T vs. +TE
**p<0.001 increase, +TTD vs. -T

TE = testosterone enanthate
TTD = transdermal patch

Snyder, P. J., H. Peachey, J. A. Berlin, P. Hannoush, G. Haddad, A. Dlewati, J. Santanna, L. Loh, D. A. Lenrow, J. H. Holmes, S. C. Kapoor, L. E. Atkinson and B. L. Strom (2000). "Effects of testosterone replacement in hypogonadal men." J Clin En-docrinol Metab 85(8): 2670-2677.

Behre, H. M., J. Bohmeyer and E. Nieschlag (1994). "Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age -matched normal controls." Clin Endocrinol (Oxf) 40(3): 341-349.

Meikle, A. W., S. Arver, A. S. Dobs, J. Adolfsson, S. W. Sanders, R. G. Middleton, R. A. Stephenson, D. R. Hoover, L. Rajaram and N. A. Mazer (1997). "Prostate size in hypogonadal men treated with a nonscrotal permeation-enhanced testosterone transdermal system." Urology 49(2): 191-196.

In the next section, Dr Cunningham reviewed the risk of developing lower urinary tract symptoms (LUTS) or BPH with testosterone replacement therapy. The study of associations of baseline total testosterone with Risk of developing symptomatic BPH in the Prostate Cancer Prevention Trial between 1993–2003 showed that in models controlled for covariates and covariates plus SHBG, men in the highest quartile of serum testosterone level had a significantly reduced risk of BPH, with no evidence of a dose-response association (Kristal, Schenk et al. 2008).

Associations of Baseline Bioavailable Testosterone with Future Risk of Symptomatic BPH, Prostate Cancer Prevention Trial, 1993–2003

Kristal AR, et al. Amer J Epidemiol 2012; 168:1416

Bioavailable testosterone	Model 1[a]		Model 2[b]		Model 3[c]	
Q1 (referent)	1.00	95% CI	1.00	95% CI	1.00	95% CI
Q2	0.92	0.68, 1.25	0.93	0.69, 1.26	0.96	0.71, 1.30
Q3	0.97	0.72, 1.31	1.00	0.73, 1.35	1.05	0.77, 1.43
Q4	0.72	0.53, 0.99	0.74	0.54, 1.04	0.81	0.57, 1.14
P for trend	0.08		0.14		0.36	

[a] Results were adjusted for age at baseline, race, body mass index, smoking status, alcohol consumption, and insulin-like growth factor binding protein 3.
[b] Results were additionally adjusted for sex hormone-binding globulin.
[c] Results were additionally adjusted for estradiol and 3-α-diol glucaronide.

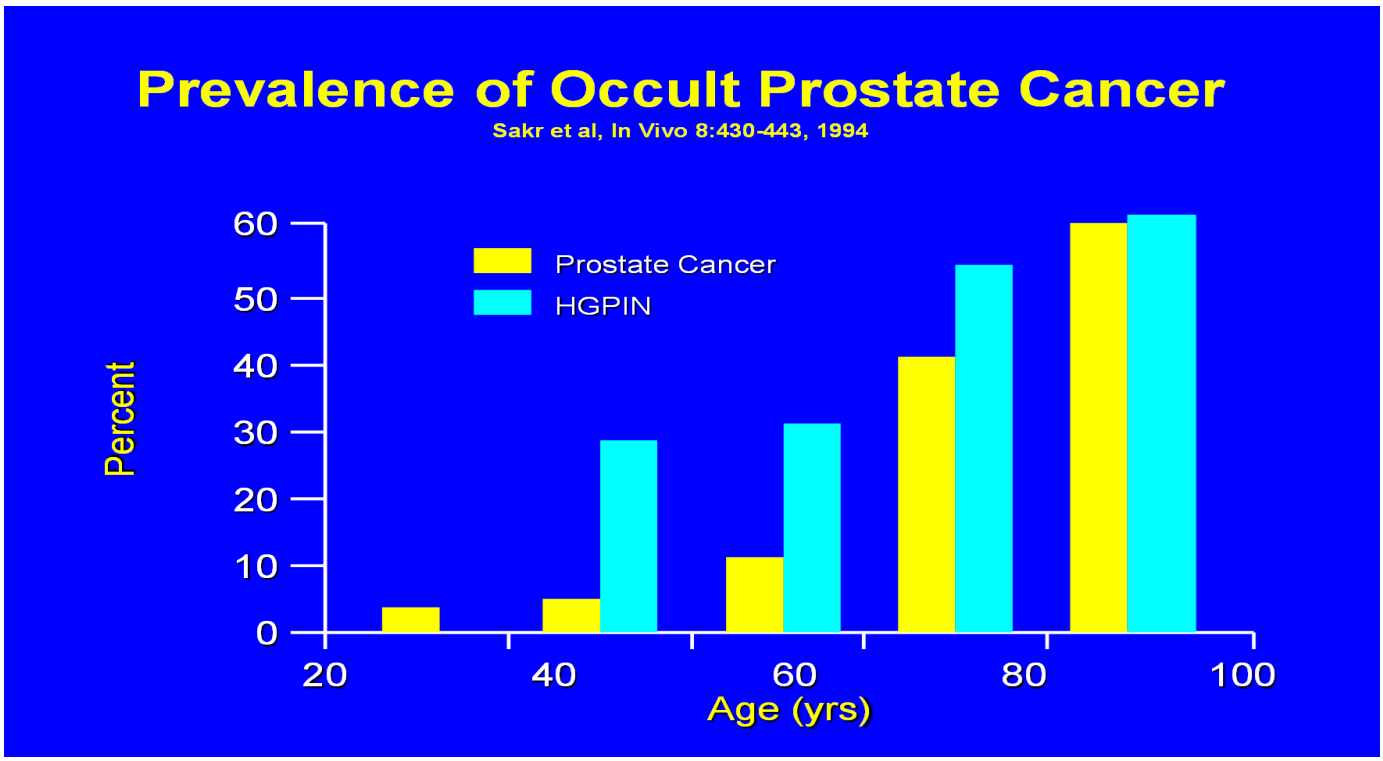
The treatment of benign prostatic hyperplasia with 5 mg of finasteride per day resulted in a significant decrease in symptoms of obstruction, an increase in urinary flow, and a decrease in pros-tatic volume, but at a slightly increased risk of sexual dysfunction. Page et al studied serum androgen concentrations, PSA and prostate volume in older, hypogonadal men with BPH treated with testosterone for 6 months (Page, Hirano et al. 2011). Combined treatment with testosterone plus dutasteride reduced prostate volume and prostate specific antigen compared to tes-tosterone only.

Jin, B., A. J. Conway and D. J. Handelsman (2001). "Effects of androgen deficiency and replacement on prostate zonal vol-umes." Clin Endocrinol (Oxf) 54(4): 437-445.

Kristal, A. R., J. M. Schenk, Y. Song, K. B. Arnold, M. L. Neuhouser, P. J. Goodman, D. W. Lin, F. Z. Stanczyk and I. M. Thompson (2008). "Serum steroid and sex hormone-binding globulin concentrations and the risk of incident benign pros-tatic hyperplasia: results from the prostate cancer prevention trial." Am J Epidemiol 168(12): 1416-1424.

Page, S. T., L. Hirano, J. Gilchriest, M. Dighe, J. K. Amory, B. T. Marck and A. M. Matsumoto (2011). "Dutasteride reduces prostate size and pros-tate specific antigen in older hypogonadal men with benign prostatic hyperplasia undergoing tes-tosterone replacement therapy." J Urol 186(1): 191-197.

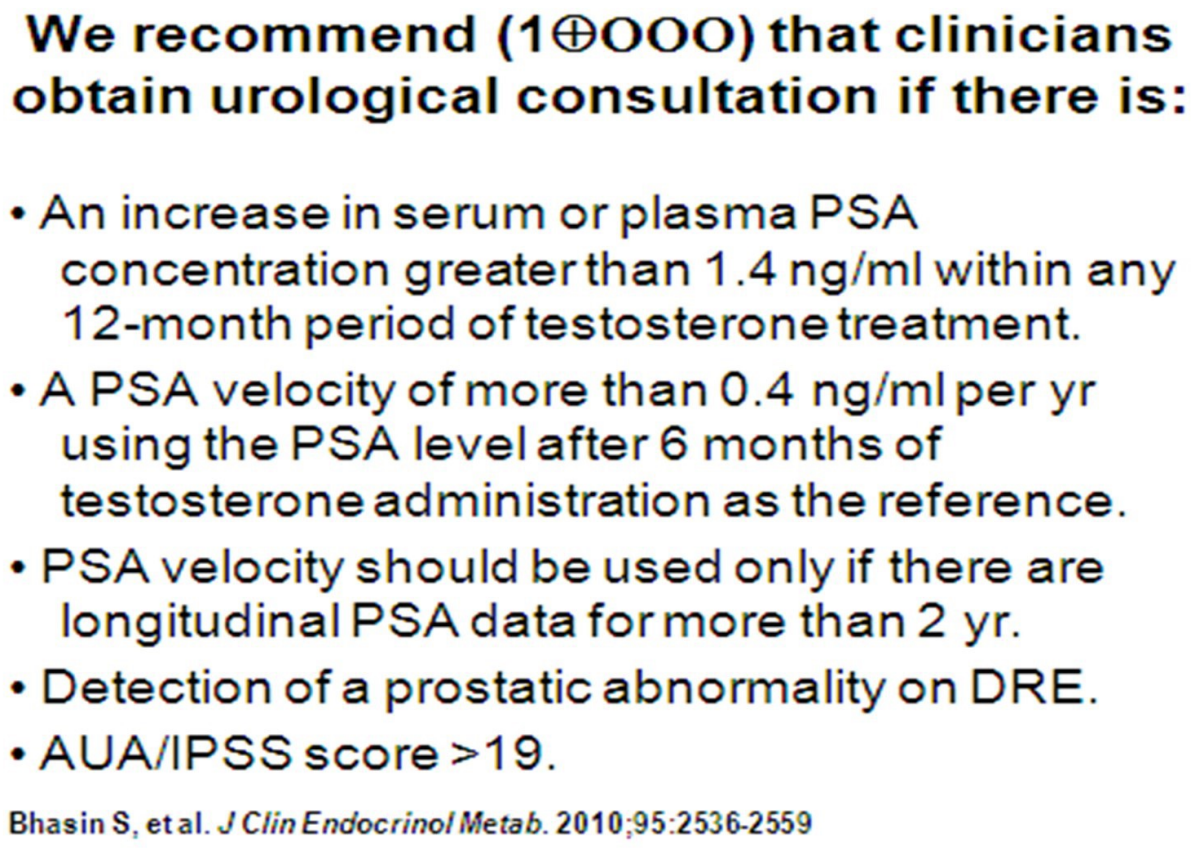
Dr Cunningham in the next section of his presentation provided an overview of the risk of de-veloping a clinical prostate cancer with testosterone replacement therapy. This is of course a big issue as there is an important increase in prostate cancer as men age. But one has also to be aware of the fact that as the men age, there is significant fall in the level of testosterone and testos-terone precursors. Therefore the increase in prostate cancer does not seems to be driven by the testosterone level in aging men. The autopsy data from 249 cases between the ages of 20-69 showed the prevalence of occult prostate cancer and high grade prostatic intraepithelial neoplasia (HGPIN) along with prostatic adenocarcinoma (Sakr, Grignon et al. 1994), the level of both increases with age to about 60%. Morgentaler et al studied total of 345 consecutive hy-pogonadal men with a prostate-specific antigen (PSA) level of 4.0 ng/mL or less. The cancer de-tection rate was 5.6%, 17.5%, 26.4%, and 36.4% for a PSA level of 1.0 or



Sakr, W. A., D. J. Grignon, J. D. Crissman, L. K. Heilbrun, B. J. Cassin, J. J. Pontes and G. P. Haas (1994). "High grade pros-tatic in-traepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases." In Vivo 8(3): 439-443.

Morgentaler, A. and E. L. Rhoden (2006). "Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less." Urology 68(6): 1263-1267.

In conclusion and based on the Endocrine Society clinical practice guideline, it is recommended clinicians to obtain urological consultation in men with androgen deficiency syndromes undergo-ing testosterone therapy in the following cases: an increase in plasma PSA concentration > 1.4 ng/ml within any 12-month period of testosterone treatment, a PSA velocity of > 0.4 ng/ml per year using the PSA level after 6-month of testosterone treatment, detection of prostatic abnor-mality on DRE, AUS/IPSS score > 19 (Bhasin, Cunningham et al. 2010).



Bhasin, S., G. R. Cunningham, F. J. Hayes, A. M. Matsumoto, P. J. Snyder, R. S. Swerdloff and V. M. Montori (2010). "Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline." J Clin Endocrinol Metab 95(6): 2536-2559.

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PRISM Advisory Board Meeting

Chicago 20th June 2014

Afternoon Session

PRISM
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Dr Adrian Dobs
Professor of Medicine and Oncology
The Johns Hopkins University School of Medicine

Testosterone and Circulating Serum Lipids

Dr. Dobs Presentation Overview:

The topic of presentation of Dr. Dobs was "Testosterone and Circulating Serum Lipids". In introduction section, Dr Dobs provided an overview of the pathophysiology of dyslipidemia. Some general statements about serum lipids and CVD is that non HDL is superior for CVD prediction than LDL-C especially when triglycerides are increased. LDL control is the mainstay of therapy and no impressive CVD event benefit may result from either HDL raising or TG lowering. Also, prevalence of CVD risk factors, e.g. obesity is extremely common. Therefore, lipid lowering medications such as statins showed effectiveness in reducing LDL about 20-55% while increase also HDL about 5-15% and decrease triglycerides about 7-30%. Other drugs such as bile acid sequestrants, Niacin, Fibric acid derivatives, Ezetimibe, and Fish oil were also effective in reducing LDL and some increasing HDL and some lowering TG. Dyslipoproteinaemia is characterized by high plasma concentrations of triglyceride-rich and apolipoprotein (apo) B containing lipoproteins, with depressed highdensity lipoprotein (HDL) and increased small dense low density lipoprotein (LDL) particle concentrations. Dysregulation of lipoprotein metabolism in the metabolic syndrome may be due to a combination of overproduction of very low density lipoprotein (VLDL) apoB, decreased catabolism of apoB containing particles, and increased catabolism of HDL apoA I particles (Chan, Barrett et al. 2014).

Chan, D. C., P. H. Barrett and G. F. Watts (2014). "The metabolic and pharmacologic bases for treating atherogenic dyslipidaemia." Best Pract Res Clin Endocrinol Metab 28(3): 369-385.

In the next session, Dr Dobs described the relationship of dyslipidemia to endogenous testosterone, which has been studies by a number of cross sectional epidemiologic trails. The "San Antonio Heart Study" showed that low testosterone was associated with high total cholesterol, LDL, and triglycerides (TG), and low HDL. The "Tromso Study" showed similar findings as low testosterone and SHBG were associated with high TG and low HDL. The "Turku Male Aging Study" showed that low testosterone correlated with low HDL, and high TC and TG. In the "Tromso Study, they looked at 2 different groups of individuals, not only the fasting TG levels but also during the day and found that low serum testosterone was associated with elevated fasting and post prandial TG during the day (Agledahl, Skjaerpe et al. 2008).

Agledahl, I., P. A. Skjaerpe, J. B. Hansen and J. Svartberg (2008). "Low serum testosterone in men is inversely associated with non-fasting serum triglycerides: the Tromso study." Nutr Metab Cardiovasc Dis 18(4): 256-262.

In the next few slides, Dr Dobs described multiple mechanisms suggested for the association of low testosterone level with the atherogenic lipid profile and then provided an overview of the effect of testosterone administration on lipid levels in the last part of her presentation.

Dr Dobs described in the summary slides the treatment approaches for dyslipidemias. In conclu-sion, dysregulation of VLDL is integral to atherogenic dyslipidemia, resulting from insulin re-sistance due to ectopic fat accumulation in visceral; LDL-cholesterol, non-HDL-cholesterol and apoB have been identified as the primary target of lipid-regulating therapy in patients at increased risk of CVD; Lifestyle modifications including weight loss, dietary modifications and exercise should be considered first; Statins are recommended as first-line lipid-regulating agent. In conclu-sion, men with lower testosterone levels are more likely to be obese, increased waist size, and non-alcoholic fatty liver. They are more likely to have an atherogenic profile of excess TG, lower HDL and higher SHBG. Lifestyle modification should be first approach and testosterone therapy may or may not be beneficial directly or indirectly. At high doses, exogenous testosterone will re-sult in a slight decline in HDL, but physiologic doses likely improve HDL.

Conclusion

- Men with lower testosterone levels are more likely to be obese, increased waist size, and non-alcoholic fatty liver
- They are more likely to have an ahterogenic profile of excess TG, lower HDL and higher SHBG
- Lifestyle modification should be first approach
- T therapy may or may not be beneficial directly or indirectly. At high doses, exogenous T will result in a slight decline in HDL, but physiologic doses likely improve HDL

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Dr. Rozhivanov Roman

National Research Center of Endocrinology

Moskow, Russia

Erectile Dysfunction in Men with Diabetes Mellitus

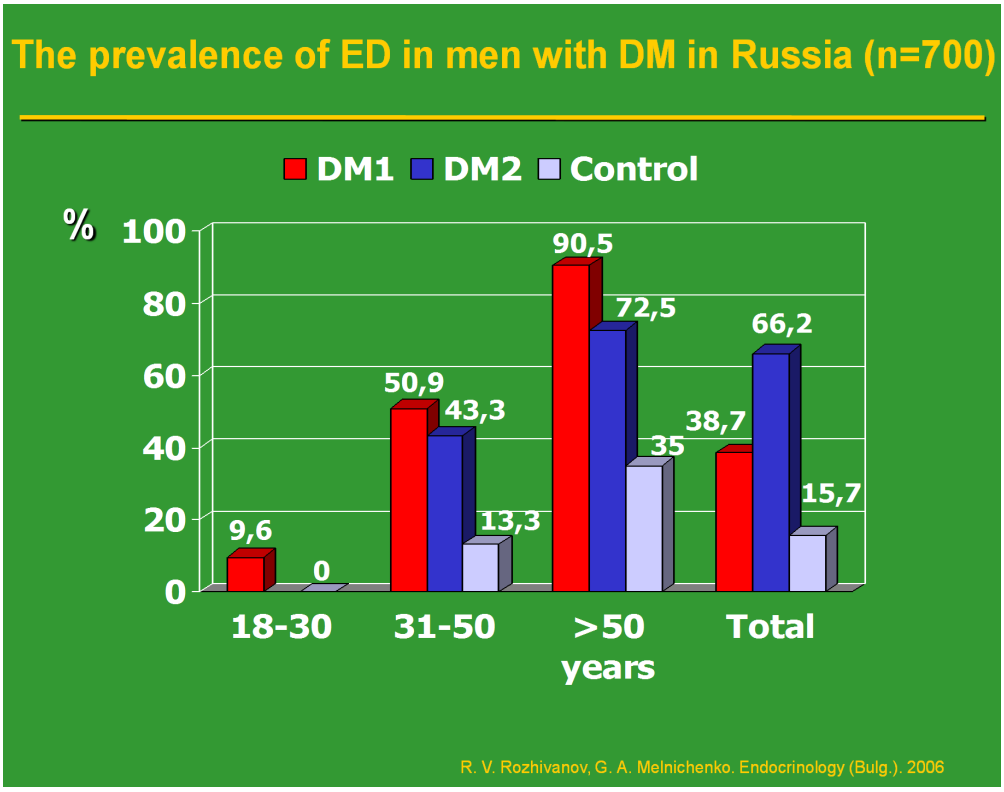
Dr. Roman Presentation Overview:

The topic of presentation of Dr. Roman was "Erectile dysfunction (ED) in men with diabetes mellitus". His presentation was in Russian language and covered 21 slides. In US, more than half of men aged 40-70 years had ED; 35% of all men in this age range had moderate to complete ED. The Massachusetts Male Aging Study (MMAS) of 1290 men was conducted from 1987 to 1989 to determine prevalence of ED and is widely regarded as one of the most comprehensive studies conducted to date in this area (Feldman, Goldstein et al. 1994). Of the men reporting some degree of ED: 19% of the men with ED(10% of the total) had complete (severe) ED, 48% (25% of the total) had moderate ED and 33% (17% of the total) had minimal ED.

Feldman, H. A., I. Goldstein, D. G. Hatzichristou, R. J. Krane and J. B. McKinlay (1994). "Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study." J Urol 151(1): 54-61.

Overall, 67% of men reporting ED in this study had moderate to complete ED. Definitions: Complete ED is defined as "unable to get and keep an erection." Moderate ED is defined as "sometimes able to get and maintain an erection." Minimal ED is defined as "usually able to get or keep an erection."

Several literatures showed that 25%-75% of men with DM has ED. The prevalence of ED was 9% in men of 20-29 years age and 95% in men 70 years age. ED presented for 5-10 years earlier in patients with DM in comparison with the general population. ED in men with DM correlated with level HbA1c, neuropathy and vasculopathy (Guay, Perez et al. 1998, Shapiro, Stansberry et al. 1998, Romeo, Seftel et al. 2000).



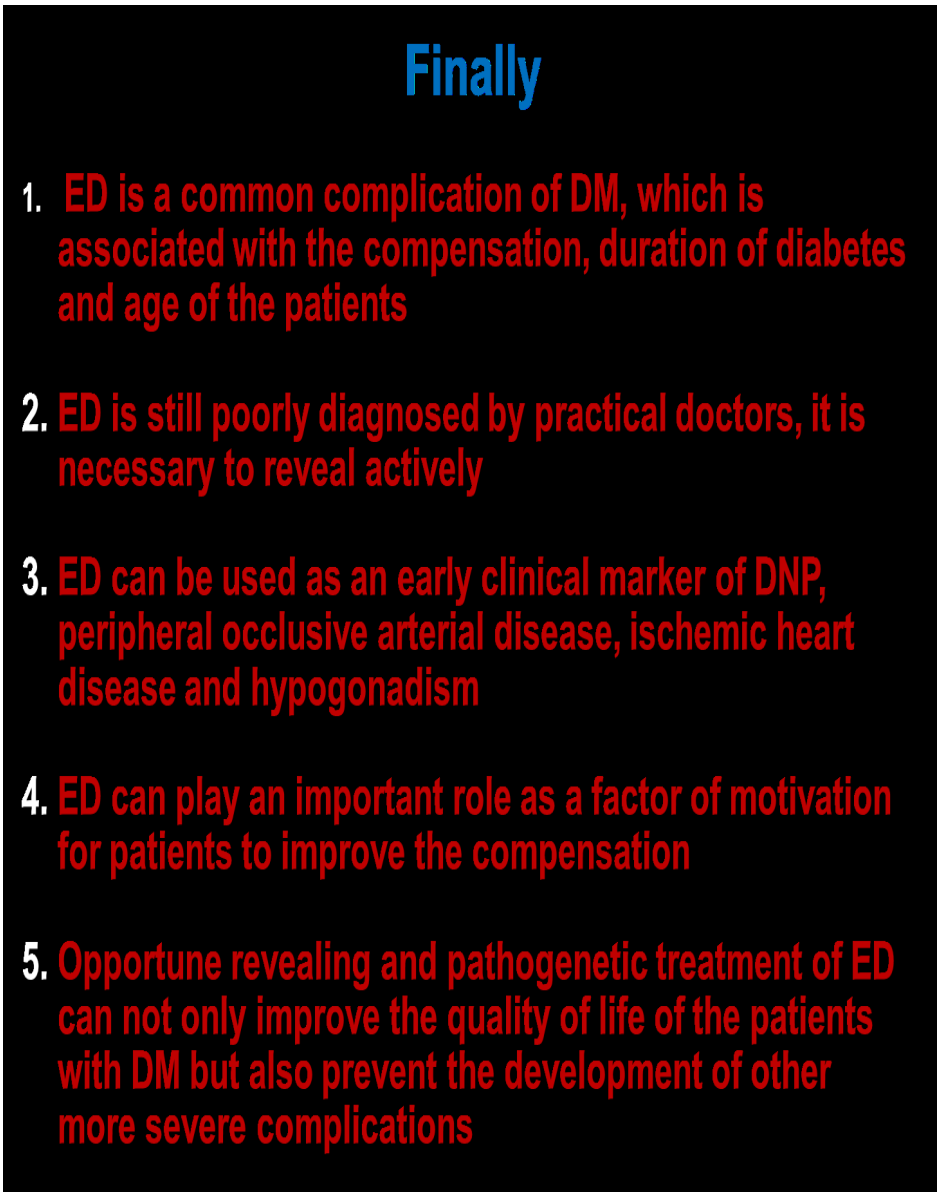
Guay, A. T., J. B. Perez and G. J. Heatley (1998). "Cessation of smoking rapidly decreases erectile dysfunction." Endocr Pract 4(1): 23-26.

Romeo, J. H., A. D. Seftel, Z. T. Madhun and D. C. Aron (2000). "Sexual function in men with diabetes type 2: association with glycemic control." J Urol 163 (3): 788-791.

Shapiro, S. A., K. B. Stansberry, M. A. Hill, M. D. Meyer, P. M. McNitt, B. A. Bhatt and A. I. Vinik (1998). "Normal blood flow response and vasomotion in the diabetic Charcot foot." J Diabetes Complications 12(3): 147-153.

ED is also the first sign and early predictor of DM complications. ED in men with DM develops earlier than first clinical signs of DNP in 46,1% of cases. ED in men with DM develops earlier than first clinical signs of peripheral occlusive arterial disease, stenocardia and myocardial infarction in 53%, 18% and 25,7% of cases, respectively. ED can be a symptom of hypogonadism and can play an important role as a factor of motivation for patients to improve the DM compensation. The prevalence of hypogonadism in men with DM2 is 2.6 times higher than in men without DM (Rozhivanov R., et al, The Aging Male, 2006).

In the last slide, Dr Roman's conclusion was that: ED is a common complication of DM, which is associated with the compensation, duration of diabetes and age of the patients; ED is still poorly diagnosed by practical doctors, it is necessary to reveal actively; ED can be used as an early clinical marker of DNP, peripheral occlusive arterial disease, ischemic heart disease and hypogonadism; ED can play an important role as a factor of motivation for patients to improve the compensation; Opportune revealing and pathogenic treatment of ED can not only improve the quality of life of the patients with DM but also prevent the development of other more severe complications.



PRISM
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Dr Marco Marcelli
Michael E. DeBakey, VA Medical Center
Baylor College of Medicine
Houston, TX 77030

Other Forms of Androgen Deficiency

Dr. Marcelli Presentation Overview:

The topic of presentation of Dr. Marcelli was "Other forms of androgen deficiency". In introduction section, Dr Marcelli provided an overview of the Androgen deficiency that is known to be associat-ed with several chronic and acute diseases. The European male aging study defined late-onset hy-pogonadism (LOH) as the presence of at least three sexual symptoms associated with a total testosterone level of less than 11 nmol per liter (3.2 ng/ml) and a free testosterone level of less than 220 pmol/L (64 pg/ml). So based on this definition, one could argue that testosterone level could be a marker of general good or bad health (Wu, Tajar et al. 2010). The more number of comorbidi-ties was associated with the lower testosterone level in the patient. A cross sectional study in Cali-fornia during 1984 -1993 on the levels of endogenous total and bioavailable testosterone in 810 men aged 24-90 years showed that the decreased level of testosterone was a consequence of the accumulation of comorbidities (Ferrini and Barrett-Connor 1998).

Wu, F. C., A. Tajar, J. M. Beynon, S. R. Pye, A. J. Silman, J. D. Finn, T. W. O'Neill, G. Bartfai, F. F. Casanueva, G. Forti, A. Giwercman, T. S. Han, K. Kula, M. E. Lean, N. Pendleton, M. Punab, S. Boonen, D. Vanderschueren, F. Labrie and I. T. Huhtaniemi (2010). "Identification of late-onset hypogonadism in middle-aged and elderly men." N Engl J Med 363(2): 123-135.

Ferrini, R. L. and E. Barrett-Connor (1998). "Sex hormones and age: a cross-sectional study of testosterone and estradi-ol and their bioavailable fractions in community-dwelling men." Am J Epidemiol 147(8): 750-754.

In the next section, Dr. Marcelli provided an overview of several acute conditions such as burn injury, Traumatic Brain Injury, and MI, which were reported to be associated with decreased testosterone levels. Although in the acute group the underlying disease process were different, the common de-nominator was that testosterone level was significantly reduced between 25 to 90%. In other chronic conditions such as sepsis, CVA, surgical stress, opioids, COPD, CHF, cancer, CKD, chronic liver disease, HIV, diabetes/obesity, and rheumatoid arthritis, the low testosterone concentrations in the severely ill male patients correlated inversely with the Acute Physiological and Chronic Health Evaluation (APACHE) score (Luppa, Munker et al. 1991). Many studies found that the decrease in testosterone was associated with simultaneous gonadotropin drop (Woolf, Hamill et al. 1985). The severity of head trauma correlated to hypogonadism, as patients who had the lowest Glasgow Coma Scale score dis-played the lowest levels of baseline and peak FSH and testosterone. Mechanism of androgen deficien-cy in burn injury showed pulsatile release of luteinising hormone in control subjects but was absent or diminished in burnt patients with low serum testosterone concentrations.

Condition	Reference	% with androgen deficiency
Burn injury	[JCEM 1985;60:658]	90/100%
TBI	[Intensive Care Med 2004;30:1051]	25%
MI	[Clin Endocrinol 1978;9:249]	T falls ~ 50% within 24 hours
Sepsis/ICU	[Clin Endocrinol 1981;34:305]/Crit Care Med 1999;27(11):2418	T falls in ~ 90% in ICU
CVA	[Neurocrit Care 2005;3:224]	39%
Surgical Stress	[JCEM 1972;35:535]	T falls ~ 50% within 24 hours
Opiods	[JCEM 2000;85:2215]	86% T < 260 ng/dL
COPD	[Am J Respir Care Med 2005;171:728]	38%
CHF	[Int J Card 87;2003:179]	25%
Cancer	Cancer 2006;106:2583	53-73%
CKD	[Metabolism 1969;18:1062]	66%
Chronic liver disease	[Br Med J 1986;293:1191	
HIV	(AJM 1988;84:611)	~ 40-50%
Diabetes/	JCEM 2004;89:5462	25-42%
Obesity	DC 2010; 33:1186–1192	40-50%
Rheumatoid Arthritis	Rheumatology 2002;41:285	15-30% depends on age

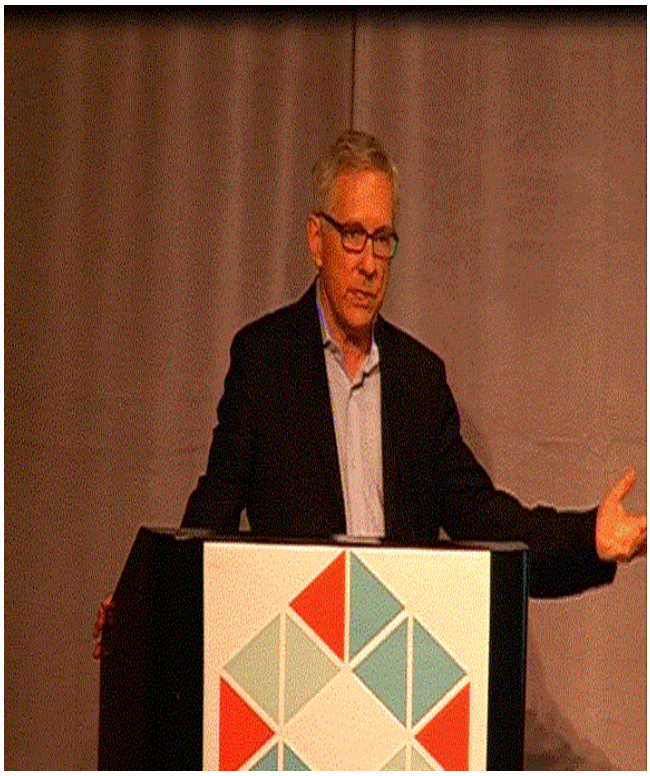
Luppa, P., R. Munker, D. Nagel, M. Weber and D. Engelhardt (1991). "Serum androgens in intensive-care patients: cor-relations with clinical findings." Clin Endocrinol (Oxf) 34(4): 305-310.

Woolf, P. D., R. W. Hamill, J. V. McDonald, L. A. Lee and M. Kelly (1985). "Transient hypogonadotropic hypogonadism caused by critical illness." J Clin Endocrinol Metab 60(3): 444-450.

In the next section of the presentation, Dr. Marcelli addressed the question of role of testosterone replacement therapy in patients affected by acute conditions causing androgen deficiency. Dr. Mar-celli personal experience was that many patients with Traumatic Brain Injury (TBI) and burn injury were severely excreted hypogonadal status. In 5 studies with total number of 136 patients, all sub-jects showed > 90% severe hypogonadism. In six severely burned male patients (>70% total body surface area), testosterone enanthate administration (200 mg/week, intramuscularly for 2 weeks), significantly increased protein synthetic efficiency up to 2-folds. Protein breakdown decreased al-most 2-fold after testosterone enanthate, resulting in an improvement in net amino acid balance (Ferrando, Sheffield-Moore et al. 2001). Effects of Oxandrolone on outcome measures in the se-verely burned patient was evaluated in a multicenter prospective randomized double-blind trial. Subjects were randomized between Oxandrolone (10 mg every 12 hours) and placebo. The conclu-sion for this initial trial was that many acute stressful conditions are associated with low testos-terone, and that replacement with testosterone or an anabolic agent has shown promises (Wolf, Edelman et al. 2006).

Ferrando, A. A., M. Sheffield-Moore, S. E. Wolf, D. N. Herndon and R. R. Wolfe (2001). "Testosterone administration in severe burns ameliorates muscle catabolism." Crit Care Med 29(10): 1936-1942.

Wolf, S. E., L. S. Edelman, N. Kemalyan, L. Donison, J. Cross, M. Underwood, R. J. Spence, D. Noppenberger, T. L. Palmieri, D. G. Greenhalgh, M. Lawless, D. Voigt, P. Edwards, P. Warner, R. Kagan, S. Hatfield, J. Jeng, D. Crean, J. Hunt, G. Purdue, A. Bur-ris, B. Cairns, M. Kessler, R. L. Klein, R. Baker, C. Yowler, W. Tutulo, K. Foster, D. Caruso, B. Hildebrand, W. Benjamin, C. Villar-real, A. P. Sanford and J. Saffle (2006). "Effects of oxandrolone on outcome measures in the severely burned: a multicenter prospective randomized double-blind trial." J Burn Care Res 27(2): 131-139; discussion 140-131.



In the last section, Dr. Marcelli provided an overview of chronic conditions such as opioids use, COPD, CHF, cancer, CKD, chronic liver disease, HIV, diabetes, obesity, rheumatoid arthritis and impact of testosterone replacement therapy on these conditions.

The meta analysis of the six trials showed a difference in the lean body mass between the testosterone group and placebo group of 1.22 kg for the random effect model and 0.51 kg for fixed effect. However, the difference was much greater in the three trials that used the intramuscular route (3.34 kg) in the post hoc analysis (Kong and Edmonds 2002).

In conclusion, Dr. Marcelli was in favour of using testosterone replacement therapy in patients affected by HIV-infection, burn injuries, and opioid use. In conclusion, the acute and chronic diseases discussed were frequently associated with hypogonadism with multiple mechanisms. For the majority of these conditions, the indication of testosterone replacement therapy has not been established due to the trial designs that was small, short and performed in a single institution.

Conclusions

- The acute and chronic diseases discussed are frequently associated with hypogonadism
- Mechanisms are multifaceted
- For the majority of these conditions it is not established if there is a role for TRT
- Studies are small, short and performed in a single institution

Kong, A. and P. Edmonds (2002). "Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis." Lancet Infect Dis 2(11): 692-699.

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Dr Joel S. Finkelstein

Endocrine Unit Massachusetts General Hospital

Associate Professor of Medicine

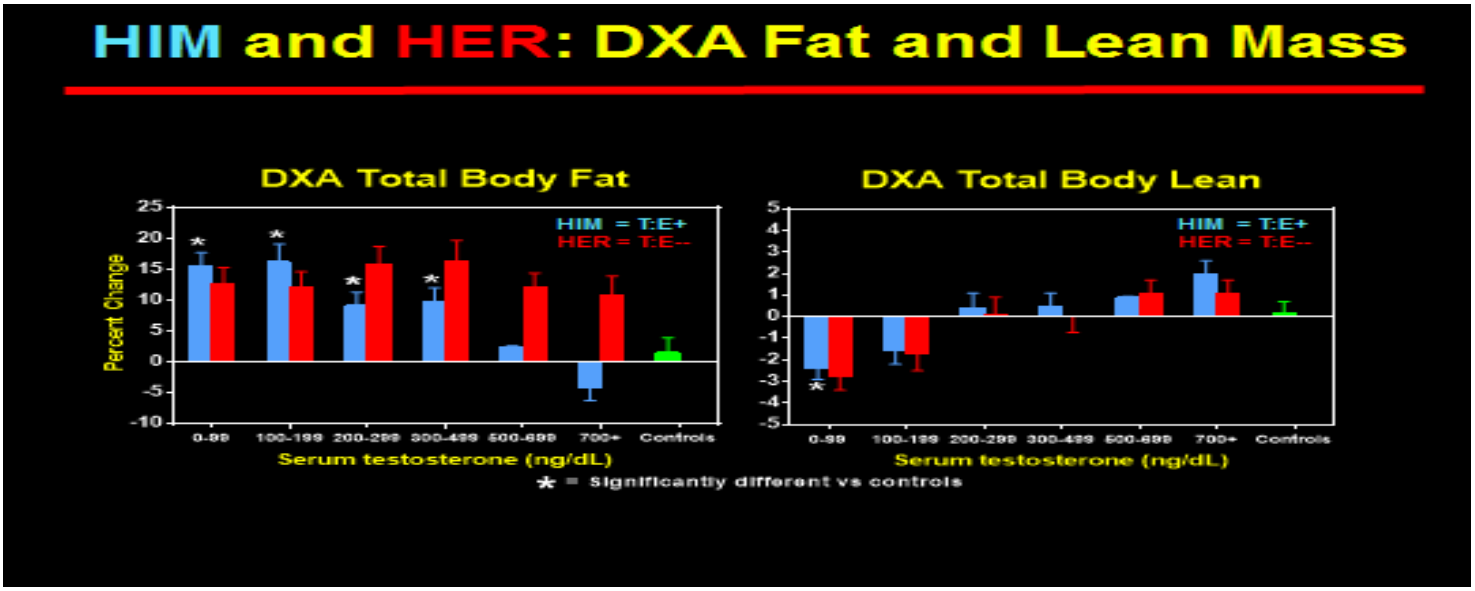
Harvard Medical School

Aromatization of T to E_2: Clinical Implications

Dr. Finkelstein Presentation Overview:

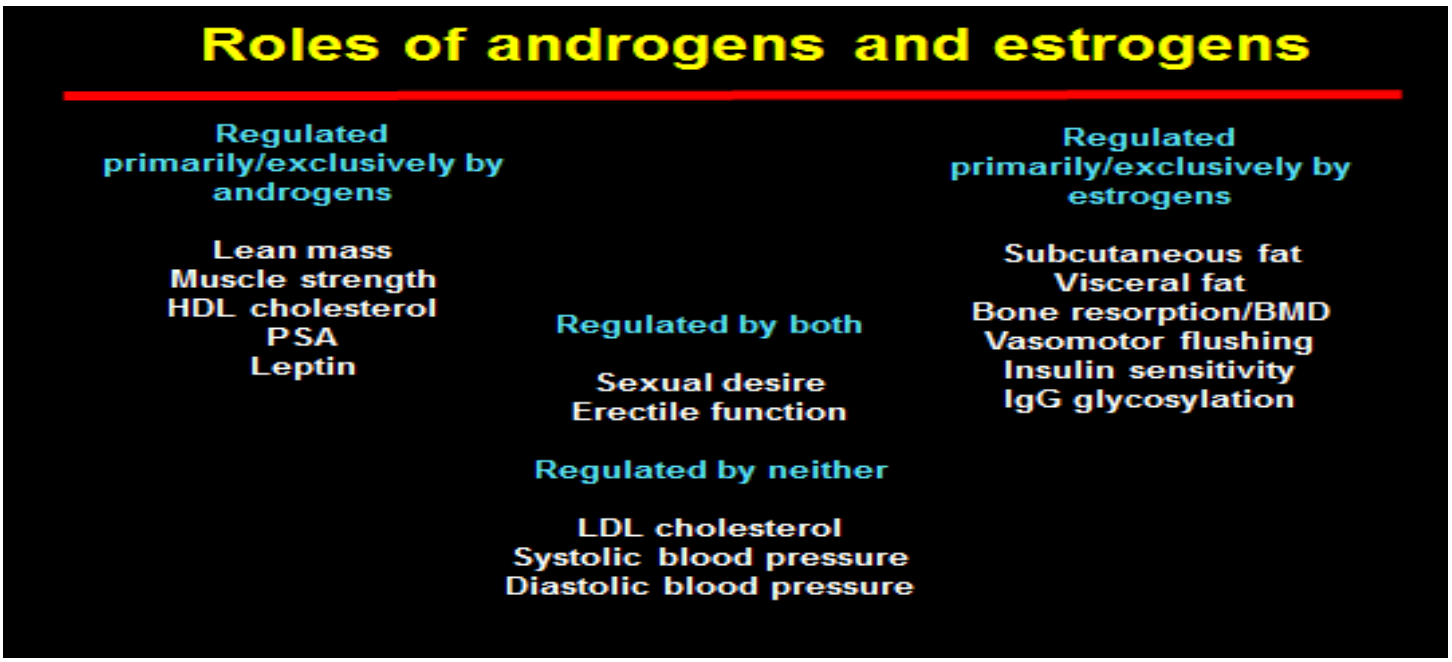
The topic of presentation of Dr. Finkelstein was "Aromatization of T to E2: Clinical Implications". In introduction section, Dr Finkelstein provided an overview of male Hypogonadism and role of estrogen. He described that the cardinal features of male hypogonadism are known to be sexual dysfunction, fatigue, decreased libido, decreased potency, increased body fat, decreased lean mass, and bone loss. Serum estradiol level was shown in recent epidemiologic studies to be correlated with fracture prevalence and bone mineral density BMD) in adult men, although the correlations are weak and no causation can be determined. Male mice and men with null mutations of their estrogen receptor (ER) or their aromatase genes have low BMD. Defects in genetic models of estrogen deficiency are likely due to reduced peak bone mass rather than increased adult bone loss. Two randomized clinical trials in adult men showed that bone resorption increased in experimental models of selective estrogen deficiency.

In next section of his presentation, Dr. Finkelstein provided an overview of the results obtained from HIM/HER cohort study. The estradiol level increased proportionally with increased doses of testos-terone in HIM but not HER cohort. That was expected as Anastrozole administration in HER cohort inhibited conversion of testosterone to estradiol. If we look at the total body fat by DXA, we see a nice dose-response in HIM group as the level of testosterone goes down, there is an increased total body fat. In HER group, the total body fat did not change even at super physiological levels of testos-terone, which shows the pure estrogenic effect on body fat. In contrast, the effect on lean body mass was the same in both HIM and HER groups, as both showed increased lean body mass proportional to the level of testosterone. This suggest that total body fat is regulated by estrogen and lean body mass is regulated by androgens. The fat compartment was regulated by estrogen as subjects in HER cohort under aromatase blocker showed significant increase in subcutaneous fat and intra-abdominal fat at high doses of testosterone.

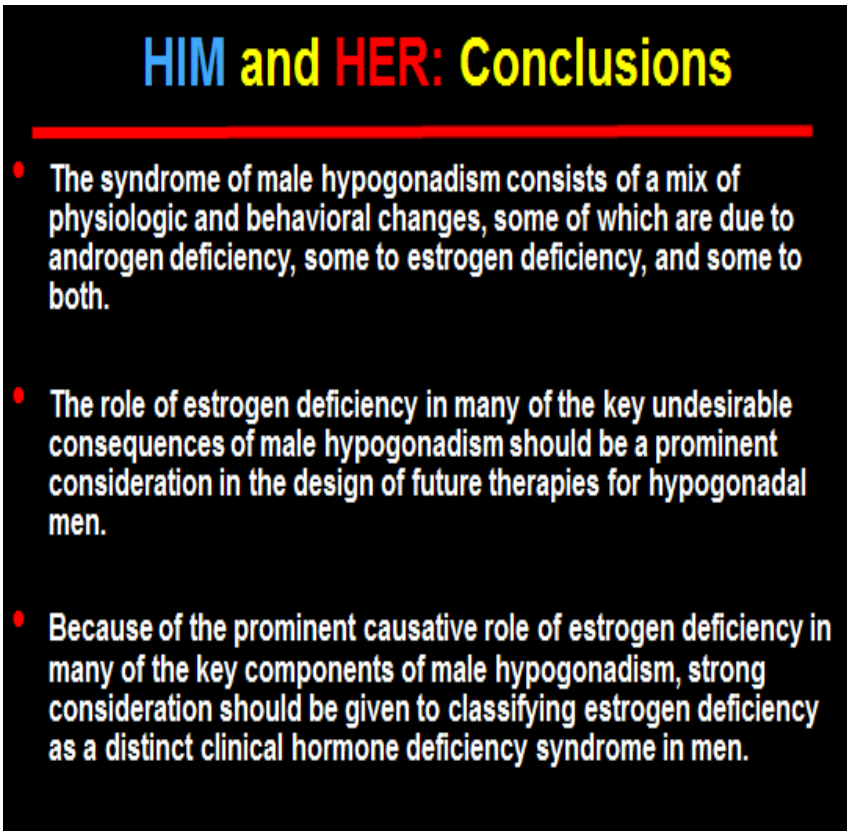


In the next few slides, Dr. Finkelstein discussed the effect on sexual function outcomes, which was one of the biggest surprises in this study. Both sexual desire and erectile function were increased dose dependently with increased testosterone levels in HIM cohort. However, both effects were partially abolished by aromatase blocker in HER group, suggestion a mixed role of androgen and estradiol. In the men treated with testosterone alone, libido appeared to decline progressively as testosterone levels fell from the middle of the reference range to castrate levels.

In summary, Dr. Finkelstein's research showed that androgens and estrogens both play important role in male hypogonadism. Lean mass, muscle strength, HDL cholesterol, PSA, and Leptin were all regulated primarily/exclusively by androgens. Subcutaneous fat, visceral fat, bone resorption/BMD, vasomotor flushing, insulin sensitivity, and IgG glycosylation were all regulated primarily/exclusively by estrogens. Sexual desire and erectile function were regulated by both while LDL cholesterol and blood pressure regulated by neither.



In conclusion, the syndrome of male hypogonadism consists a mix of physiologic and behavioral changes, some of which are due to androgen deficiency, some to estrogen deficiency, and some to both. The role of estrogen deficiency in many of the key undesirable consequences of male hypogonadism should be a prominent consideration in the design of future therapies for hypogonadal men. Because of the prominent causative role of estrogen deficiency in many of the key components of male hypogonadism, strong consideration should be given to classifying estrogen deficiency as a distinct clinical hormone deficiency syndrome in men. Dr. Finkelstein finished his presentation by asking the question of "What makes a real man, is that androgens or estrogens"? His answer was that while it is clear that androgens are important to make a real man, however, estrogen is what that makes a Super Man.



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Dr Stephanie T. Page

Associate Professor of Medicine
Department of University of Washington

Seattle, WA

The Use of Testosterone as a Male Contraceptive

Dr. Page Presentation Overview:

The topic of presentation of Dr. Page was "The Use of Testosterone as a Male Contraceptive". In the introduction section, Dr Page provided an overview of the most important global health issue that is an astronomical population growth. This seems to be out of control due to high fertility rates. The fertility rates have an incredible and exponential effect on population growth, so very small differences in fertility rates result in very significant different growth in population. There is no question from a variety of many public health studies that contraceptive choice and availability has been increasing, which resulted in decreased population growth. One may ask if there is a need for additional contraceptives.

The data from 1995 (UNFPA/WHO/World Bank, 1995), even before the explosion of testosterone therapy, showed 100 million acts of intercourse daily with 1 million conceptions. The study showed high number of unplanned pregnancy of about 500,000/day, many led to induced abortion, which often took place in unsafe conditions and led to maternal death. So there is clearly a need for additional contraceptive and the question is why we need a male contraceptive.

The study in US on various methods of contraception in 1998 showed that men contraception was used in one third of total methods and the trend was increased over time, suggesting more men were willing to use male contraceptive methods (Piccinino and Mosher 1998). The study by Weston et al in Australia showed that many men, in fact up to 75%, are willing to use male contraceptive (Weston, Schlipalius et al. 2002), consistent with other studies.

Percentage of Contraceptive Users by Current Method in U.S.[1]

Method	1982	1988	1995
Tubal Ligation	23	28	28
Vasectomy	11	12	11
Pill	28	31	27
Condom-male	12	15	20
Injectable/Implant	-	-	4
IUD	7	2	1
Diaphragm	8	6	2
Withdrawal	2	2	3
Periodic abstinence	4	2	3
Foam,sponge, female condom	3	1	1

1. Piccinino and Mosher. *Fam Plan Per* 1998 30:4-10.

In the next section of the presentation, Dr Page provided an overview of the Hormonal Male Con-traceptives and the mechanism of action of hormonal contraceptives

Piccinino, L. J. and W. D. Mosher (1998). "Trends in contraceptive use in the United States: 1982-1995." Fam Plann Per-spect 30(1): 4-10, 46.

Weston, G. C., M. L. Schlipalius, M. N. Bhuinneain and B. J. Vollenhoven (2002). "Will Australian men use male hormonal contracep-tion? A survey of a postpartum population." Med J Aust 176(5): 208-210.

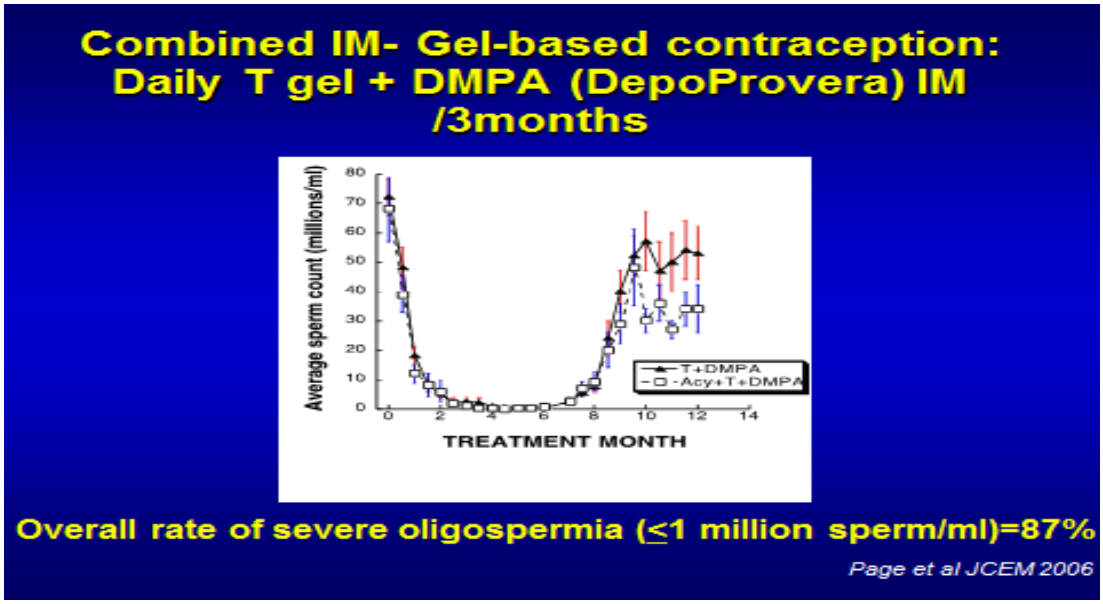
Dr. Page described in next part of her presentation an overview of clinical studies conducted on the testosterone alone prepara-tions as male hormonal contraceptive. The early studies were done with high doses of testosterone by WHO in 271 healthy fertile men at 10 centers worldwide receiving tes-tosterone enanthate at 200 mg IM/weekly (WHO 1990). The results showed 157 men (cumulative rate at 6 months 65%) became azoospermic in three consecutive semen samples.

The conclusion was that hormonal regimens that induce azoospermia can provide highly effective, sustained, and re-versible male contraception with minimum side-effects. In 2nd WHO trial, testosterone weekly injec-tion was tested in 399 men in 15 countries (WHO 1996). There were 391 cases that showed suppres-sion of sperm count to < 5 million/mL and entered efficacy phase (95% efficacy). The study defined that the minimum sperm count for acceptable efficacy should be < million count/ml. In summary, the testosterone alone male contraceptive showed variable rate of azoospermia (60% Caucasian to 90 % Asian), about 95% overall contraceptive efficacy, 1-3 month delay in onset, mild short-term side effects, and unknown long-term side effects/benefits. The non-uniform azospermia and requirement for weekly intramuscular injections kept this product away from marketplace.

WHO (1990). "Contraceptive efficacy of testosterone-induced azoospermia in normal men. World Health Organization Task Force on methods for the regulation of male fertility." Lancet 336(8721): 955-959.

WHO (1996). "Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men." Fertil Steril 65(4): 821-829.

In the next section of the presentation, Dr Page provided an overview of the efficacy of hormonal male contraceptives based on combination of testosterone with progestin. A combined long acting injectable testosterone undecanoate with depo medroxyprogesterone acetate (DMPA) given intra-muscularly at 8 week intervals to Chinese men showed more efficacy in suppressing spermatogenesis than the efficacy of testosterone undecanoate alone (Gu, Tong et al. 2004). Dr Page studied forty-four healthy men randomized to receive testosterone gel (100 mg daily) plus DMPA (300 mg/3 months) or acyline (300 microg/kg.2 wk x 12 wk) plus testosterone gel and DMPA. Thirty-eight men completed the 24-week treatment protocol. All men had dramatic suppression of spermatogenesis with the overall rate of severe oligospermia, which was defined as <1 million sperm/ml, was 87%. The addition of acyline did not significantly accelerate spermatogenic suppression or improve rates of severe oligospermia. There were no serious adverse events, and there were minimal changes in weight, serum lipids, and prostate-specific antigen (Page, Amory et al. 2006).



Gu, Y. Q., J. S. Tong, D. Z. Ma, X. H. Wang, D. Yuan, W. H. Tang and W. J. Bremner (2004). "Male hormonal contracep-tion: effects of injections of testosterone undecanoate and depot medroxyprogesterone acetate at eight-week inter-vals in chinese men." J Clin Endocrinol Metab 89(5): 2254-2262.

Page, S. T., J. K. Amory, B. D. Anawalt, M. S. Irwig, A. T. Brockenbrough, A. M. Matsumoto and W. J. Bremner (2006). "Testosterone gel combined with depomedroxyprogesterone acetate is an effective male hormonal contraceptive regi-men and is not enhanced by the addition of a GnRH antagonist." J Clin Endocrinol Metab 91(11): 4374-4380

In the next section, Dr Page discussed the topic of acceptability of experimental male contraceptives. The men who were selected to participate in these trials rated the methods "as expected, or better than expected" with no change in quality of life, although reported slight increase in frequency and quality of sex life (Sjogren and Gottlieb 2001).

In summary, male hormonal contraceptives exhibited reversible inhibition of spermatogenesis in most, but not all men (85-90% < 1 million/ml) and no safety issues and minimal short-term side effects. These agents would be accepted by men and partners and all is needed now is final pharma-ceutical company push" to get the products to market.

Sjogren, B. and C. Gottlieb (2001). "Testosterone for male contraception during one year: attitudes, well-being and quality of sex life." Contraception 64(1): 59-65.

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Dr Aleksey Zilov

Sechenev First Moskow State Medical University

Russia

A Trial of Testosterone Therapy in Diabetic Patient with Low Testosterone

Dr. Zilov Presentation Overview:

The topic of presentation of Dr. Zilov was "A trial of testosterone therapy in diabetic patients with low testosterone". In the introduction section, Dr Zilov provided an overview of the hypogonadism prevalence and its association with aging and metabolic syndrome. A 2003 report by the Institute of Medicine (IOM) surveyed the literature on the benefits and risks of testosterone replacement therapy in older men. It concluded that based on recent studies, hypogonadism in men may be more prevalent than previously thought and is strongly associated with metabolic syndrome, and it could be a risk factor for type 2 diabetes and cardiovascular disease. Other clinical studies have shown that testosterone replacement therapy in hypogonadal men improves metabolic syndrome indicators and cardiovascular risk factors. Based on current knowledge, testosterone replacement therapy is unlikely to pose major health risks in patients without prostate cancer and may offer substantial health benefits (Miner and Seftel 2007).

Miner, M. M. and A. D. Seftel (2007). "Testosterone and ageing: what have we learned since the Institute of Medicine report and what lies ahead?" Int J Clin Pract 61(4): 622-632.

In the next section of his presentation, Dr. Zilov provided an overview of clinical studies conducted in his institute and Russia. Studies conducted in twenty one men (aged 25-65 year) that had a glucose tolerance test and assessment of insulin sensitivity showed strong correlation between insulin re-sistance and the testosterone response to human chorionic gonadotropin (hCG). Baseline testos-terone levels correlated with the increase in testosterone after hCG administration. These data sug-gested that insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men (Pitteloud, Hardin et al. 2005). The HIM study to evaluate the prevalence of hypogonadism in males (2162 patients) revealed that the crude prevalence rate of hypogonadism was 38.7% and the odds ratios for having hypogonadism were significantly higher in men with hypertension (1.84), hy-perlipidemia (1.47), diabetes (2.09), and obesity (2.38) (Mulligan, Frick et al. 2006).

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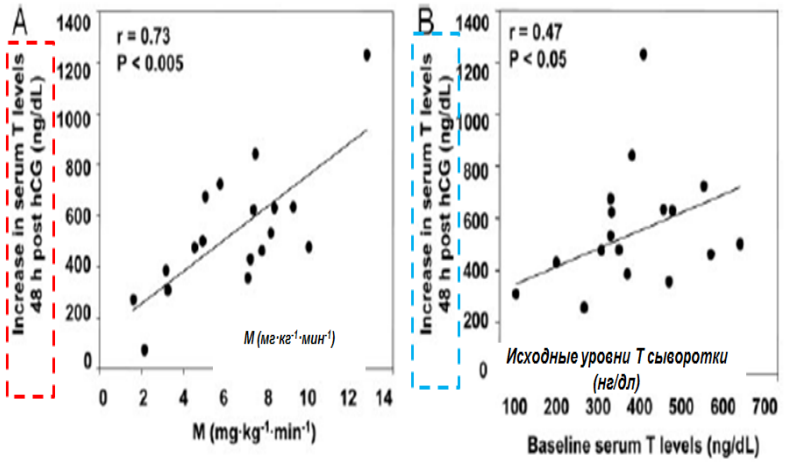
The Journal of Clinical Endocrinology & Metabolism 90(5):2636–2641

doi: 10.1210/jc.2004-2190

Increasing Insulin Resistance Is Associated with a Decrease in Leydig Cell Testosterone Secretion in Men

Nelly Pitteloud, Megan Hardin, Andrew A. Dwyer, Elena Valassi, Maria Yialamas, Dariush Elahi, and Frances J. Hayes

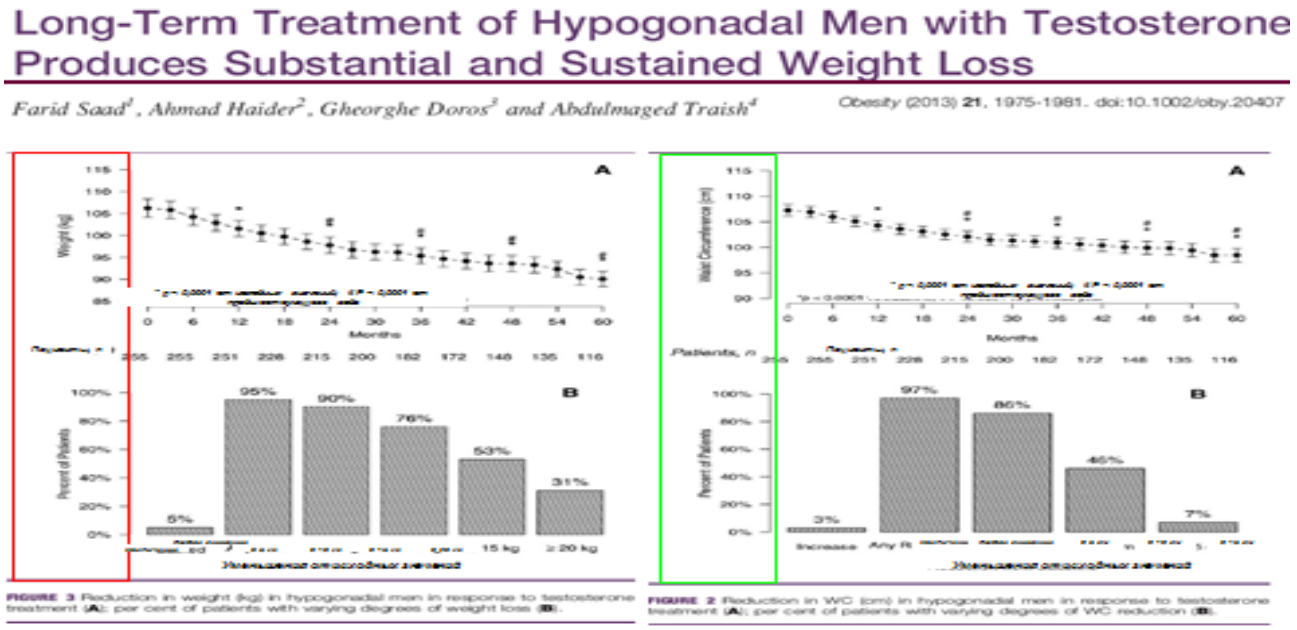


Pitteloud, N., M. Hardin, A. A. Dwyer, E. Valassi, M. Yialamas, D. Elahi and F. J. Hayes (2005). "Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men." J Clin Endocrinol Metab 90(5): 2636-2641.

Mulligan, T., M. F. Frick, Q. C. Zuraw, A. Stemhagen and C. McWhirter (2006). "Prevalence of hypogonadism in males aged at least 45 years: the HIM study." Int J Clin Pract 60(7): 762-769.

In the next section, Dr. Zilov described the issue of lack of consensuses in Russia for the treatment of androgen deficiency. The European guidelines are being used in Russia, which works but it is not certain if these recommendations would work in Russian populations in terms of clinical efficacy. Many epidemiological studies have shown that BMI and abdominal obesity correlates with low total testosterone, free testosterone, and DHEA.

The possible mechanism could be increased androgen clearance in adipocytes, aromatization of androgens, increased production of IL-1beta, T NF-alpha, and decreased production of LH and GRH. Based on these publications, Dr. Zilov conducted a clinical trial in patients with type 2 diabetes in his clinic. The cohorts with testosterone enanthate showed de-crease in fat mass as predicted. The long-term treatment of hypogonadal men with testosterone produced substantial and sustained weight loss and BMI in an uncontrolled, observational study and the improvements were progressive over the full 5 years of the study (Saad, Haider et al. 2013).



Saad, F., A. Haider, G. Doros and A. Traish (2013). "Long-term treatment of hypogonadal men with testosterone pro-duces substantial and sustained weight loss." Obesity (Silver Spring) 21(10): 1975-1981

In the last section of his presentation, Dr. Zilov described the next step or what physicians may get with testosterone re-placement therapy as there is no available guideline in his country. Based on trial data published by Isidori et al (Isidori, Giannetta et al. 2005) and Jones et al (Jones, Arver et al. 2011)(TIMES2-study), transdermal testosterone replacement thera-py was associated with beneficial effects on insulin resistance, total and LDL cholesterol, Lpa, and sexual health in hy-pogonadal men with type 2 diabetes and/or Metabolic syndrome over a 6 month period. The data from Boyanov (Boyanov, Boneva et al. 2003) showed tremendous decrease in HbA1C level, however there was oth-er changes in medical treatments that could have helped improving patient's condition.

Isidori, A. M., E. Giannetta, D. Gianfrilli, E. A. Greco, V. Bonifacio, A. Aversa, A. Isidori, A. Fabbri and A. Lenzi (2005). "Effects of testosterone on sexual function in men: results of a meta-analysis." Clin Endocrinol (Oxf) 63(4): 381-394.

Jones, T. H., S. Arver, H. M. Behre, J. Buvat, E. Meuleman, I. Moncada, A. M. Morales, M. Volterrani, A. Yellowlees, J. D. How-ell and K. S. Chan-ner (2011). "Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syn-drome (the TIMES2 study)." Diabetes Care 34(4): 828-837.

Boyanov, M. A., Z. Boneva and V. G. Christov (2003). "Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency." Aging Male 6(1): 1-7.

The results from Kapoor (Kapoor, Goodwin et al. 2006) study showed small improvement suggesting other factors are also involved in poorly controlled diabetes patients. In hypogonadal patients as shown previously, the testosterone replacement therapy had significant impact on lowering waist circumference and improving insulin resistance.

In conclusion, Dr. Zilov mentioned that he is in process of designing a randomized controlled trial similar to the one published by the Dr Grossmann in Australia evaluating the effect of testosterone treatment on glucose metabolism in men with type 2 diabetes (Gianatti, Dupuis et al. 2014).

Kapoor, D., E. Goodwin, K. S. Channer and T. H. Jones (2006). "Testosterone replacement therapy improves insulin re-sistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes." Eur J Endocrinol 154(6): 899-906.

Gianatti, E. J., P. Dupuis, R. Hoermann, B. J. Strauss, J. M. Wentworth, J. D. Zajac and M. Grossmann (2014). "Effect of testos-terone treatment on glucose metabolism in men with type 2 diabetes: a randomized controlled trial." Diabetes Care 37(8): 2098-2107.

Closing Speech

By

Prof. Frans Debruyne

Dr Jean Paul Deslypere

THANK YOU!