PRISM

POSTGRADUATE INTERNATIONAL SCHOOL OF MEN'S HEALTH

Meeting Highlights

PRISM ADVISORY BOARD

in Washington DC, USA

16th January 2015

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Welcome and Introduction

Dear Colleagues,

Good morning dear colleagues and welcome to the third advisory board of PRISM, the Post-graduate International School of Men's Health. PRISM is a relatively new initiative, which was started a little bit more than one year ago. The PRISM has two facets, one is “The Course” that has been conducted eight times in Bruges, Belgium, Singapore, and Sydney in 2014. Secondly, we have an advisory board that was held in Washington DC in 2013, Chicago in 2014 at the endocrine society meeting, and today in Washington DC in 2015.

PRISM is an evolving concept and will be an independent organization. We are looking for academic affiliation to provide objective training and education and also discuss and exchange ideas in an open environment. This is necessary as I think after 30 or 40 years, we still don't know a lot and there are still a lot of open questions. The first part of today’s meeting objective is to get more information about DHT .

The second objective, which is also very important for all of us is to address a couple of questions about topics which are very hot and controversial and any general practitioners, endocrinologists, and urologists are confused as we are also confused. So better we should align our thinking as much as possible so then we can go back with clear information, not necessarily guidelines. Questions such as “Does LOH indeed exist? What is the lowest normal T level? Are there new ways of administration of testosterone? Is testosterone safe?” Also we have to be very cautious between correlation and causation and lastly I think we are still medical doctors and must take into consideration that the aim of the medical profession is, To Improve Patients Survival!

Jean-Paul Deslypere M.D. Ph.D., FFPM (Hon)

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WELCOME NOTE

Dear Colleagues,

It is my pleasure to welcome you to the Scientific Advisory Board Meeting organized by the Post Graduate International School of Men's Health (PRISM), a new educational initiative supported by an unconditional grant of Besins Healthcare.

We hope that this Advisory Board meeting will give you the opportunity to discuss some of the challenges and opportunities associated with androgen therapy in hypogonadal men.

We are pleased that renowned KOLs from different countries around the globe are joining us and hope that the knowledge obtained during this Advisory Board meeting will improve our understanding about male hormones.

Lastly, some practical information and event details are enclosed in this welcome package. We hope you have a fruitful meeting and enjoy your stay in the beautiful city of Washington DC, USA.

Yours Sincerely,

Chairman

Marco Marcelli

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PRISM PROGRAM

Morning Sessions

Registration at 7:50am **Date: 16th January 2015**

8:00 AM- 8:10 AM Welcome and introduction

Jean-Paul Deslypere M.D. Ph.D., FFPM (Hon) Global Head Medical Affairs Besins Healthcare

8:10 AM- 8:15 AM Opening remarks

Marco Marcelli M.D., / Moderator

SESSION I : CONDITIONS ASSOCIATED WITH LOW T OR ABNORMAL T/E2 ratio: IS THERE A ROLE FOR ANDROGEN REPLACEMENT ?

8:15 AM- 8:40 AM The role of anabolic steroids in cancer cachexia

Jose Garcia M.D. Ph.D., Baylor College of Medicine, Houston TX, USA

8:40 AM- 8:55 AM Q & A

8:55 AM- 9:20 AM Androgen therapy for hypercatabolism of severe burns

David Handelsman M.D. Ph.D., ANZAC Research Institute, University of Sydney, Australia

9:20 AM- 9:35 AM Q & A

9:35 AM- 9:50 AM COFFEE BREAK

SESSION II : CONDITIONS ASSOCIATED WITH LOW T OR ABNORMAL T/E2 ratio: IS THERE A ROLE FOR ANDROGEN REPLACEMENT ?

9:50 AM- 10:15 AM Physiopathology and treatment of gynecomastia: role of dihydrotestosterone

Marco Marcelli M.D., Baylor College of Medicine, Houston TX, USA

10:30 AM- 10:55 AM Consequences of low DHT

Michael Zitzmann M.D., Munster University Medical School, Munster, Germany

10:55 AM- 11:10 AM Q & A

SESSION III: CURRENT CONTROVERSIES -I- LATE ONSET HYPOGONADISM (LOH)

11:10 AM- 11:35 AM Andropause: A fiction in search of a definition

David Handelsman M.D. Ph.D., ANZAC Research Institute, University of Sydney, Australia

11:35 AM- 11:50 AM Q & A

11:50 AM- 12:15PM Natural history of hypogonadism in the European Male Ageing Study (EMAS)

Frederick Wu M.D. Ph.D., University of Manchester, Manchester, UK

12:15 PM- 12:30 PM Q & A

12:30 PM- 1:15 PM LUNCH

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SESSION I: CONDITIONS ASSOCIATED WITH LOW TESTOSTERONE OR ABNORMAL T/E2 ratio: Is There a Role for Androgen Replacement?

The Role of Anabolic Steroids in Cancer Cachexia

Jose Garcia M.D. Ph.D.

Associate Professor, Baylor College of Medicine, Houston TX, USA

Michael E. DeBakey Veterans Affairs Medical Center, Diabetes and Metabolism

Departments of Medicine and Molecular and Cell Biology, Huffington Center on Aging

The lifetime probability of developing cancer is 1 in 2 men and 1 in 3 for women.[1] The US Mortality data also indicates that a high percentage of death (22.8%) occurs due to cancer, that is the 2nd rank after heart diseases.[2] Beside the high prevalence and mortality, cancer is associated with many symptoms that affects quality of life of patients. Cachexia, a complex metabolic syndrome characterized by loss of muscle with/without loss of fat mass, is observed in 80% of all patients suffering from various forms of cancer.[3] There is strong correlation between survival rate of cancer patients and weight body loss.[4] Hypogonadism is also very prevalent in cancer population and many symptoms are of hypogonadism such as sexual dysfunction, depressed mood, fatigue, and weakness are common symptoms seen in cancer patients. Burney and Garcia described the pathogenic mechanism of cancer-induced hypogonadism (Figure 1).[5]

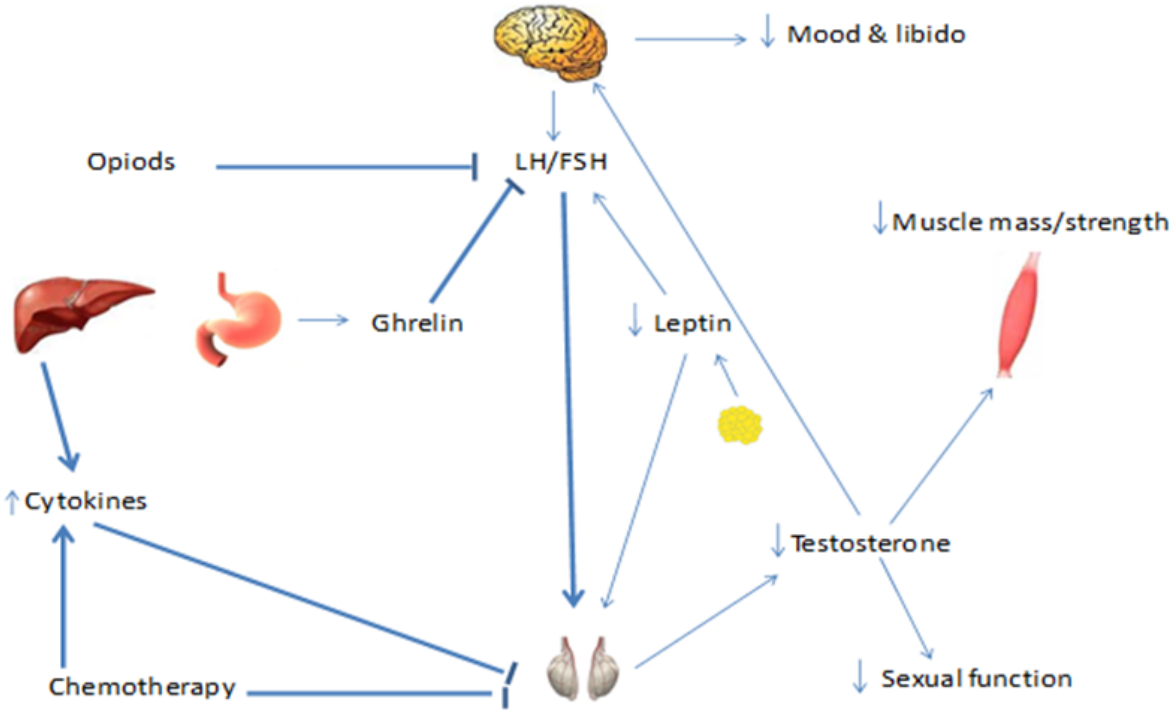

Figure 1. Hypogonadism in Cancer: Pathogenesis

Bioavailable testosterone is the most accurate method to assess hypogonadism in cancer patients.[6] Low testosterone levels are associated with anorexia, high IL-6 and low IGF-1 levels. Cancer-cachexia patients have higher inflammation and lower testosterone, grip strength, functional status, erectile function, fat mass, and aLBM.[5, 7]

A preliminary Randomized, double-blinded trial of testosterone replacement for fatigue in male hypogonadic patients with advanced cancer reveled that TRT improved FACIT-fatigue scores compared to placebo and also the emotional well-being and performance status improved significantly in the testosterone group while Sexual Desire Inventory score approached significance. [8] In conclusion, in hypogonadal men with advanced cancer, testosterone replacement showed a trend toward improved quality of life outcomes, such as FACIT-F and sexual desire inventory compared to placebo.[8] Larger interventional studies are warranted before routine testosterone replacement can be recommended.

Androgen Therapy for Hypercatabolism of Severe Burns

David Handelsman M.D. Ph.D.

ANZAC Research Institute, Concord Hospital, University of Sydney, Australia

Severe burn is among most devastating non-fatal injuries and the 4th most common cause of injury globally. In 2004, 11 million people required medical care due to burn injuries which resulted in 0.3 million deaths, similar to the incidence of cancers and greater than Tb or HIV.[9]

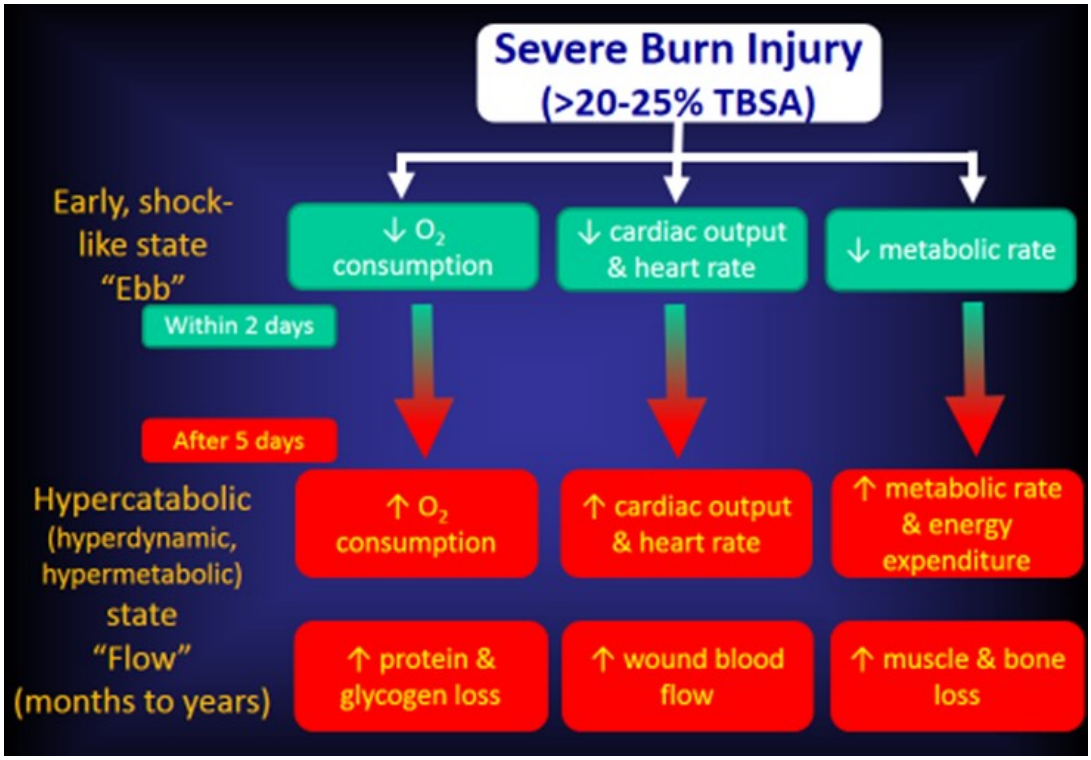

Figure 2. Systemic Metabolic Response to Severe Burn Injury

Severe burn injuries often lead to a dramatic systemic metabolic response known as the hypercatabolic response, characterized by a hyperdynamic circulatory response with massive protein and lipid catabolism, total body protein loss, severe loss of muscle and bone mass, multiple organ failure, peripheral insulin resistance, increased energy expenditure, increased body temperature, and stimulated synthesis of acute phase proteins located in the liver and intestinal mucosa (Figure 2).[10]

The pharmacotherapy of burns hypercatabolism includes use of androgens such as oxandrolone and testosterone. Oxandrolone, a synthetic derivative of testosterone, has been used in adult patients with severe thermal injury to enhance lean body mass accretion, restore body weight, and accelerate wound healing. In randomized clinical studies, oxandrolone 10 mg orally twice/ day improved wound healing, restored lean body mass, and accelerated body weight gain. During the rehabilitation period, oxandrolone therapy with adequate nutrition and exercise improved lean body mass, increased muscle strength, and restored body weight. [11]

DHT, the most potent and natural androgen that is non-hepatotoxic, non-alkylated, and available in gel form is another potential anabolic agent and clinical trial of DHT gel for burns hypercatabolism is being investigated.

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6. Morley JE, et al., Validation of a screening questionnaire for androgen deficiency in aging males, Metab. 2000; 49 (9):1239-42.

7 Garcia et al., Hypogonadism in male patients with cancer, Cancer 2006: 15; 106(12):2583-91.

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SESSION II: CONDITIONS ASSOCIATED WITH LOW TESTOSTERONE OR ABNORMAL T/E2 ratio: Is There a Role for Androgen Replacement?

Physiopathology and Treatment of Gynecomastia: Role of Dihydrotestosterone

Marco Marcelli M.D.

Baylor College of Medicine, Houston TX, USA

The Gynecomastia is a common endocrine disorder in which there is a benign enlargement of breast tissue in males. The prevalence of asymptomatic gynecomastia is 60% to 90% in neonates, 50% to 60% in adolescents, and up to 70% in men aged 50 to 69 years. [1,2]

Gynecomastia is thought to be caused by an altered ratio of estrogens to androgens mediated by an increase in estrogen production, a decrease in androgen production, or a combination of these two factors (Figure 3). Estrogen acts as a growth hormone to increase the size of male breast tissue. [3]

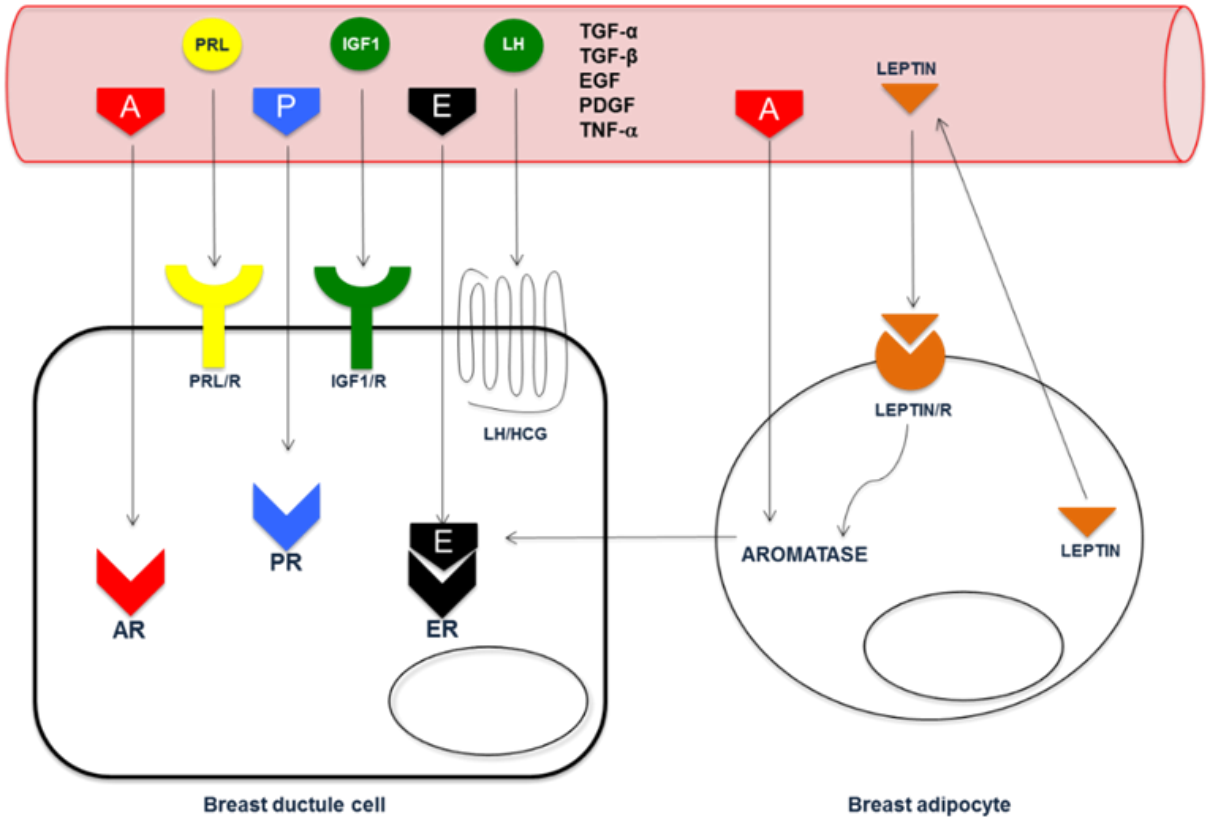

Figure 3. Physiopathology of Gynecomastia

Levels of free serum testosterone are decreased in patients with gonadal failure, which can be primary (Klinefelter syndrome, mumps orchitis, castration) or secondary (hypothalamic and pituitary disease). Androgen resistance syndromes due to impaired activity of enzymes involved in the biosynthesis of testosterone can also be associated with gynecomastia. [4]

Pharmacotherapy of gynecomastia includes estrogen receptor modifiers such as (Tamoxifen or Raloxifene, Clomiphene), androgens (Testosterone, Dihydrotestosterone, Sanazol), and aromatase inhibitors (Testolactone and Anastrozole). Dihydrotestosterone (DHT) seems a rational choice for pharmacotherapy of gynecomastia as it is not aromatizable, exerts pure androgenic function, increases the A/E ratio, exerts negative feedback, and decreases gonadotropin secretion and endogenous testosterone.

A clinical study of treatment of persistent pubertal gynecomastia in four pubertal boys with dihydrotestosterone heptanoate (200-400 mg IM at 2-4 week, intervals for 4 month) for 16-24 months showed that all four boys responded, had a 63 to 78% reduction in breast size and an acceptable cosmetic result. [5]

In another clinical trial study, the clinical and endocrine parameters in a group men with persistent idiopathic gynaecomastia (of more than 18 months duration) was studies before and during the administration of percutaneous DHT. Local administration of DHT was followed by the complete disappearance of gynaecomastia in 10 patients, partial regression in 19 and no change in 11 patients after 4 to 20 weeks of percutaneous DHT (125 mg twice daily). The T/E2 ratio decreased from 231 +/- 20 to 164 +/- 27 (P less than 0.05) while the T + DHT/E2 ratio increased significantly (P less than 0.02) to a normal mean value (day 15: 354 +/- 57). [6]

In conclusion, DHT treatment is safe for adult individuals and is a rational therapy for patients with gynecomastia, except when there is a h/o prostate cancer. According to uncontrolled small studies, DHT is effective, but a placebo controlled study in large number of patients is necessary to confirm its efficacy and safety.

Consequences of Low DHT

Michael Zitzmann M.D

Internal Medicine Endocrinology, Diabetology, Andrology Sexual Medicine (FECSM)
Munster University Medical School, Munster, Germany

In men, testosterone plays a key role in the development of male reproductive tissues such as the testis and prostate as well as promoting secondary sexual characteristics such as increased muscle, bone mass, and the growth of body hair. In addition, testosterone is essential for health and well-being as well as the prevention of osteoporosis.[7] Therefore, it is not surprising to see that many organs are the target of testosterone and its metabolites such as dihydrotestosterone (DHT) as shown in Figure 4.

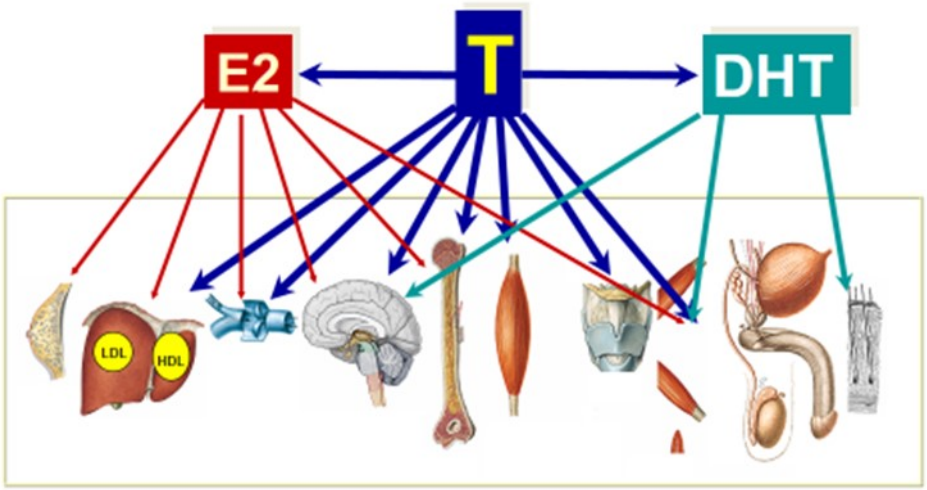

Figure 4. Target Organs of Testosterone and its Metabolites

Differentiation of external genitalia. The external genitalia of males and females are identical in the first seven weeks of gestation. In males, from seven weeks, active differentiation towards the male phenotype occurs moderated by testosterone and its conversion to dihydrotestosterone (DHT) by 5-alpha reductase (present in the cells of external genitalia and urogenital sinus). 5α-reductase (5α-R) deficiency is an important cause of ambiguous genitalia in genetic males. A 6 month old boy with 5α-reductase deficiency, has been treated effectively with DHT gel following 5 months administration.[8]

Optimal androgen levels are a biomarker for survival because older men with midrange levels of T and DHT had the lowest death rates from any cause, whereas those with higher DHT had lower IHD mortality.[9] In a cross-sectional analysis, men with low levels of androgens (T and DHT) and SHBG, but not estrogens (E2, E1) had more than 2-fold higher odds of exhibiting the metabolic syndrome.[10]

In summary, testosterone and DHT are needed for sexual function and eugonadal men need DHT for normal sexual functioning. The male bone needs testosterone and estradiol, possibly also DHT but the prostate needs relatively small amounts of androgens. Also the male brain needs androgens T and/or DHT for spatial cognition.

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Andropause: A Fiction in Search of a Definition

David Handelsman M.D. Ph.D.

ANZAC Research Institute, University of Sydney, Australia

There is a growing interest in the use of testosterone therapy for middle-aged and older men. This interest has led to the definition of a new condition, termed 'andropause', meaning the putative somatic consequences of gradually falling blood testosterone concentrations during male aging. The current status and prospects for androgen therapy in middle-aged and older men should be evaluated critically from the perspective of male reproductive health during aging.[1]

When andropause occurs, it is considered to be a deficiency state in which the hormone testosterone goes below the normal range for an aging male. Figure 5 shows andropause criteria with respect to total blood testosterone concentration under different regulatory environment.

"Andropause" criteria	Australia 2000	Europe 2005/9	USA 2006/10
CLINICAL COMPONENT			
Non-specific symptoms	Any	Any	Any
Distinguish pathological basis	Yes	No	No
HORMONAL CONFIRMATION			
No treatment	TT > 8nM	TT >12 nM	Nil
Treatment "trial"	Nil	TT 8-12 nM	Nil
Treatment	TT < 8 nM	TT < 8 nM	TT<10.4 nM
REGULATORY STATUS	Governs reimbursement	Nil	Nil

Figure 5. Andropause Criteria with Respect to Total Testosterone Concentration in Australia, Europe, and USA

Androgen misuse is the systematic over-prescribing for unproven medical indications. The androgen misuse is increasingly evident for male ageing and some other clinical conditions. Further trials for new indications for androgens require reliable safety data, but rising costs may make it increasingly attractive to circumvent the need for evidence by promoting off-label mass marketing. Despite ongoing androgen misuse and abuse, testosterone remains under-prescribed for younger men with classical androgen deficiency that frequently remains undiagnosed.[2]

In the absence of any new indications, off-label testosterone prescribing has increased in most countries in 2000-2011, especially over the last half of the period. The increased testosterone prescribing appears to be primarily for older men and driven by clinical guidelines that endorse testosterone prescribing for age-related functional androgen deficiency (andropause).[3]

In conclusions, andropause" ("late onset hypogonadism") is a fiction in search of a definition. It is a non-disease "Sick Eugonadal Syndrome" while testosterone deficiency is a clinical diagnosis with a pathological basis, and confirmed by hormone assays - not the other way around. The age effects on androgen status are due to impact of co-morbidities (obesity, CVD, organ failure, depression etc) and the biological plausibility for CV safety signals but the data is weak due to study limitations (scope, quality, design, size) and labelling changes required for testosterone products to reflect these interpretations.

Natural History of Hypogonadism in the European Male Ageing Study (EMAS)

Frederick Wu M.D. Ph.D.
University of Manchester, Manchester, UK

The European Male Ageing Study (EMAS) is a multicentre prospective longitudinal observational study of over 3000 men recruited designed to examine the prevalence, incidence and geographical distribution of gender-specific and general symptoms of ageing in men, including their endocrine, genetic and psychosocial predictors. [4] The men aged 40–79 years were recruited from eight European centres: Florence (Italy), Leuven (Belgium), Lodz (Poland), Malmö (Sweden), Manchester (UK), Santiago de Compostela (Spain), Szeged (Hungary) and Tartu (Estonia) followed up for 4.3 years, using standardised methods, translated questionnaires and central labs including tandem mass spectrometry on a single fasting morning blood sample (Figure 6).[4,5]

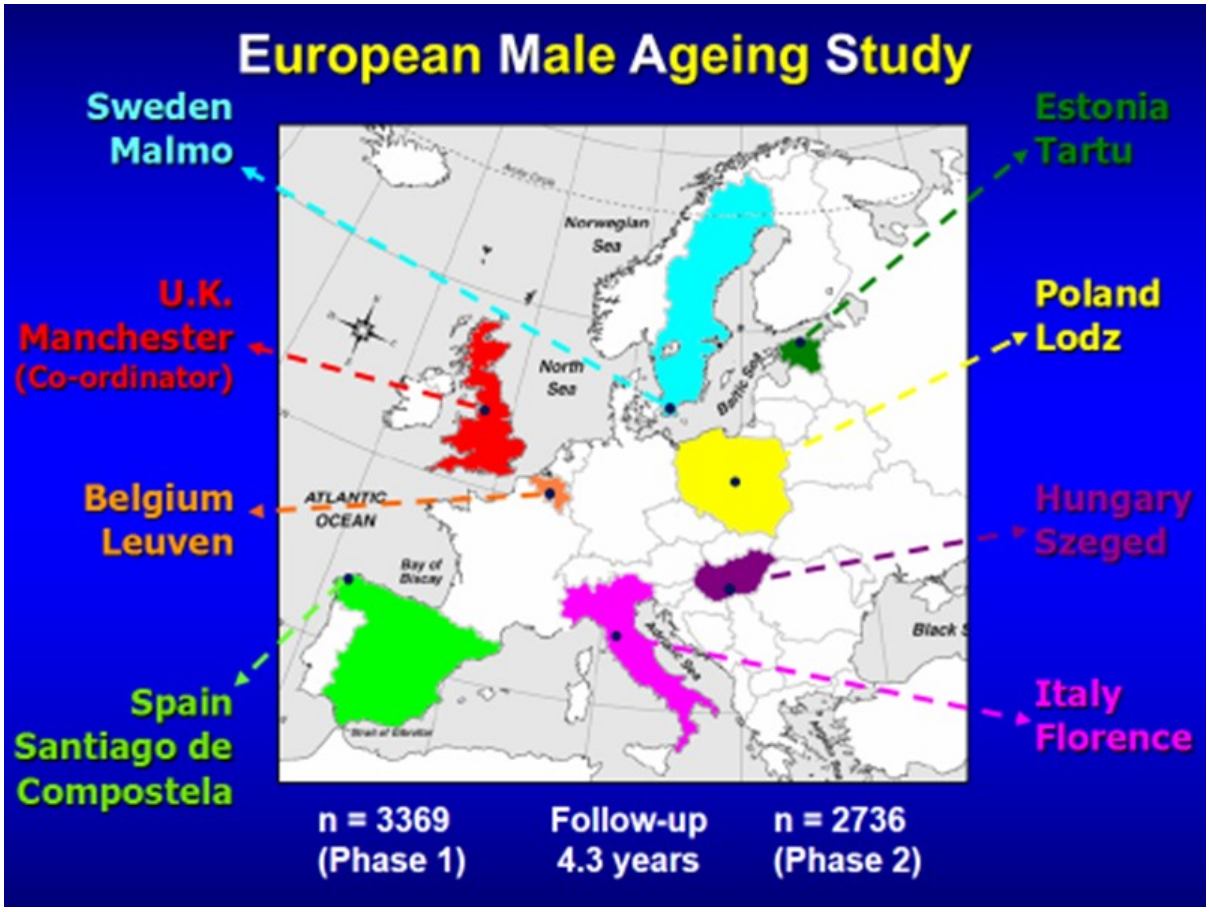

Figure 6. The European Male Ageing Study (EMAS) Participant Countries

Prospective epidemiological data from a general population cohort confirmed two divergent routes of HPT axis dysfunction that underlie the age-related decline in testosterone: Primary hypogonadism, and Secondary hypogonadism. The population of >3000 men aged 40 – 80 year, using T and LH thresholds were segregated based on level of T and LH to replicate clinical practice to: Eugonadal (normal T and LH), Primary hypogonadism (low T and high LH), and Secondary hypogonadism (low T and normal or low LH), and Compensated hypogonadism (normal T but high LH). At baseline, 78% of the general population were eugonadal, 12% can be classified as biochemically hypogonadal. A relative small (1.7%) cohort of men with primary hypogonadism and around 10% each for secondary and compensated hypogonadism, thus the secondary hypogonadism is 6x more common than primary hypogonadism (Figure 7).[6]

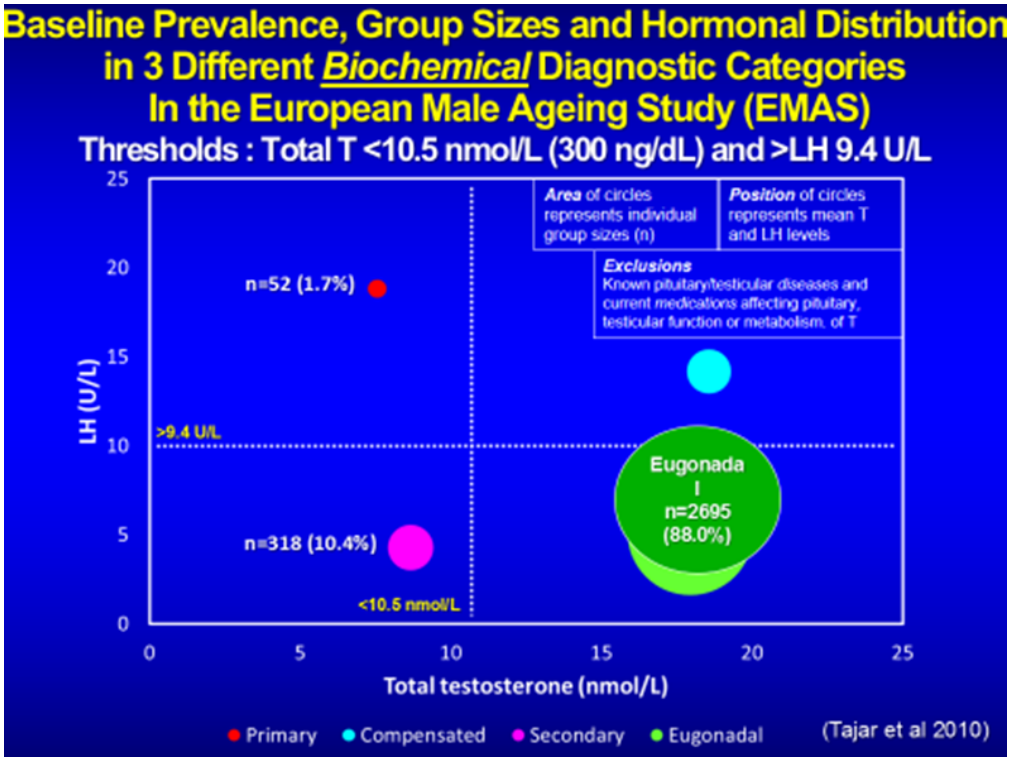

Figure 7. The European Male Ageing Study (EMAS) Participant Countries

Secondary Hypogonadism was the most common form of biochemical hypogonadism with prevalence of 10-11% and incidence of 1.2% P.A. Secondary hypogonadism from chronic but reversible from hypothalamic suppression, is clearly related to obesity and associated with development and worsening of sexual symptoms. It is reversible in up to 41% and predicted by obesity and weight gain.[6] Primary hypogonadism was the least common form of biochemical hypogonadism with prevalence of 1.7-2.1% and incidence rate of 0.27% P.A. from eugonadal. It is reversible up to 16.7% potentially and predicted by higher age, smoking and co-morbidity. The transition from eugonadism to compensatory hypogonadism (with an of incidence 1.2% P.A, prevalence of 9%) is predisposed by higher age (>70), poor health and pain (but not obesity). [6]

References:

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Afternoon Sessions

SESSION IV: CURRENT CONTROVERSIES -II- DEFINITIONS OF LOWER LIMIT OF NORMAL T

1:15 PM- 1:40 PM	Issues with testosterone measurements and reference ranges in men Christina Wang M.D., Harbor UCLA Medical Center, Torrance CA, USA
1:40 PM- 1:55 PM	Q & A
1:55 PM- 2:20 PM	Defining low testosterone in old men Bu Yeap M.D. Ph.D., University of Western Australia, Crawley Western Australia
2:20 PM- 2:35 PM	Q & A

SESSION V: NEW DELIVERY METHODS

2:35 PM- 3:00 PM	Novel approaches for the delivery of Testosterone Ronald Swerdloff M.D., Harbor-UCLA Medical Center, Torrance CA
3:00 PM- 3:15 PM	Q & A
3:15 PM- 3:30 PM	COFFEE BREAK

SESSION VI: CURRENT CONTROVERSIES -III- COMPLICATIONS OF TRT

3.30 PM- 3.55 PM	Use of TRT in men with LOH: a precautionary tale Abraham Morgentaler M.D., Men's Health, Dept. Urology, Harvard Medical School, Boston MA, USA
3:55 PM- 4:10 PM	Q & A
4:10 PM- 4:35 PM	TRT in ageing men: a potentially dangerous cult Steve Nissen M.D., Cleveland Clinic, Cleveland OH, USA
4:35 PM- 4:50 PM	Q & A
4:50 PM	ADJOURNMENT
6:00 PM	DINNER

SESSION IV: CURRENT CONTROVERSIES -II- DEFINITIONS OF LOWER LIMIT OF NORMAL TESTOSTERONE

Issues with Testosterone Measurements and Reference Ranges in Men

Christina Wang M.D.

Harbor UCLA Medical Center, Torrance CA, USA

Accurate testosterone testing is essential to the right diagnosis and the appropriate treatment such as diagnosis of hypogonadism and monitoring of treatment in men and diagnosis of androgen excess and low androgens syndromes in women.[1] Serum testosterone has a diurnal variation (highest in the morning) and morning samples are useful to compare with reference ranges determined from samples drawn in the morning in young men.

Dr Wang's group examined serum testosterone levels in pedigreed samples by four commonly used automated immunoassay instruments and compared results with measurements performed by liquid chromatography-tandem mass spectrometry (LC-MSMS). The immunoassays were capable of distinguishing eugonadal from hypogonadal males if adult male reference ranges have been established in each individual laboratory. The lack of precision and accuracy, together with bias of the immunoassay methods at low serum T concentrations, suggests that the current methods cannot be used to accurately measure testosterone in females or serum from prepubertal subjects.[2,3] The variability of total testosterone measurement results among MS assays was substantially smaller than that reported for immunoassays. The type of sample preparation may affect assay precision, thus standardizing assays can further reduce the variability of measurement results.[4]

Accurate testosterone testing can be achieved through standardization. New references for men across countries being developed by Center for Disease Control (CDC, USA) and PATH (Partnership in Accurate Testing of Hormones). CDC has a reference method for testosterone in place and provides high quality serum materials to labs and assay manufacturers to calibrate their assays.

The mean absolute bias of routine mass spectrometry methods to the CDC reference method dropped by about half from 2007 to 2011 indicating a significant improvement in testosterone accuracy (Figure 8).[5]

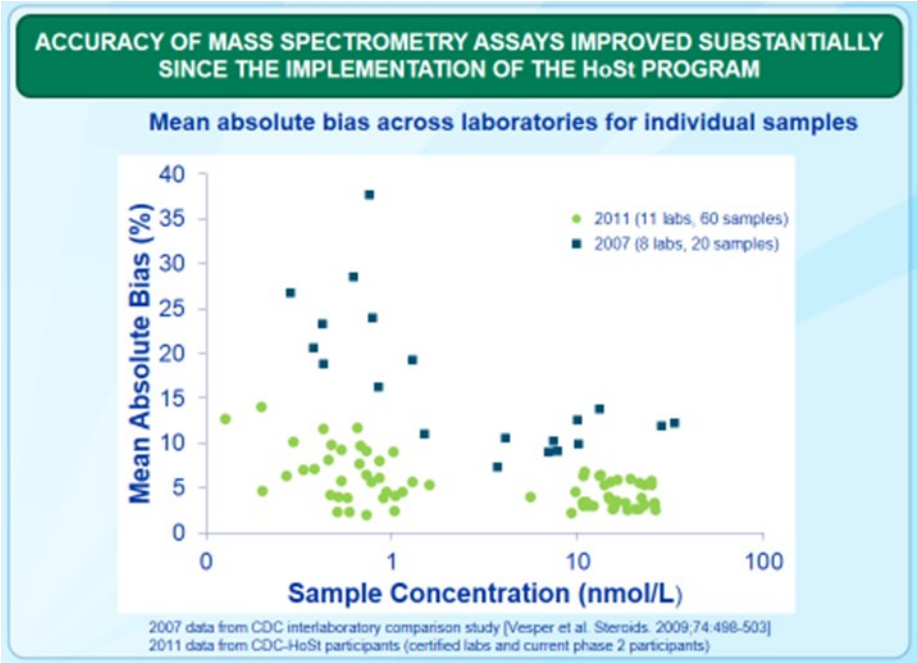

Figure 8. Implementation of the CDC HoSt Program and Accuracy of MS Assays

There are no generally accepted lower limits of normal for free testosterone for the diagnosis of hypogonadism. However, a free testosterone level below 220 pmol/L (64 pg/mL) can provide supportive evidence for T treatment. Serum testosterone in adult men generally accepted as 300-1000 ng/dl (10 to 35 nmol/l).[6]

Defining Low Testosterone in Old Men

Bu Beng Yeap MBBS, FRACP, PhD
School of Medicine and Pharmacology, University of Western Australia
Crawley Western Australia

As men grow older, their testosterone levels decline, while the risk of ill-health increases (diabetes, cardiovascular disease, frailty, osteoporosis, dementia, death). The Endo Society guideline for testosterone therapy (2010) recommended making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels.[7]

It recommended testosterone therapy for men with symptomatic androgen deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. [7]

Management of male infertility and/or androgen deficiency requires accurate hormonal measurements with valid reference intervals. Reference ranges are essential for partitioning testosterone levels into low or normal and making the diagnosis of androgen deficiency. Clinical trial in 124 healthy reproductively normal men at age, 21-35 year showed testosterone reference range of 10.4 to 30.1 nmol/L (300-867 ng/dl).[8] In another study, the established reference ranges for mean ± SD, median, and 2.5th percentile values total testosterone (TT) in a community-based sample of 456 men (19-40 years) were 723.8±221.1(25.1 ±7.7 nmol/L), 698.7 (24.2 nmol/L), and 348.3-1197 ng/dl (12.1-41.5 nmol/L) for TT.[9]

Increasing age, higher body mass index and waist to hip ratio, dyslipidemia, diabetes, and higher LH were independently associated with lower levels of T and DHT. [10] In a reference group of 394 men aged 76.1 ± 3.2 year reporting excellent or very good health with no history of smoking, diabetes, cardiovascular disease, cancer, depression, or dementia, the 2.5th percentile for T was 6.4 nmol/liter (184 ng/dl); DHT, 0.49 nmol/liter; and E2, 28 pmol/liter. Applying these cutoffs to all 3690 men, those with low T or DHT had an increased odds ratio for frailty, diabetes, and cardiovascular disease. Men with both low T and DHT had a higher odds ratio for these outcomes (Figure 9).[10,11]

	Frailty N=563	Diabetes N=571	CVD N=1,362
Variable	OR (95% CI) p value	OR (95% CI) p value	OR (95% CI) p value
T ≤12.1 nmol/L (348 ng/dL) N=1,673	1.82 (1.51,2.19) <0.001	2.22 (1.85,2.67) <0.001	1.23 (1.08,1.41) <0.001
T ≤6.40 nmol/L (184 ng/dL) N=190	2.70 (1.94,3.74) <0.001	2.76 (2.00,3.81) <0.001	1.61 (1.20,2.17) <0.001
DHT ≤0.49 nmol/L (14.2 ng/dL) N=204	1.67 (1.18,2.37) <0.001	2.50 (1.82,3.43) <0.001	1.47 (1.10,1.97) 0.01
E2 ≤27.55 pmol/L (7.5 pg/mL) N=126	1.16 (0.73,1.84) 0.54	0.88 (0.52,1.47) 0.62	0.97 (0.67,1.41) 0.89
Low T (≤6.40 nmol/L) and DHT (≤0.49 nmol/L) N=74	3.28 (2.01,5.36) <0.001	2.77 (1.69,4.56) <0.001	1.78 (1.11,2.85) 0.02
Low T (≤6.40 nmol/L) and E2 (≤27.55 pmol/L) N=51	1.44 (0.75,2.77) 0.27	1.09 (0.51,2.34) 0.83	1.69 (0.96,2.97) 0.07
Low DHT (≤0.49 nmol/L) and E2 (≤27.55 pmol/L) N=27	2.30 (1.00,5.26) 0.05	0.72 (0.21,2.39) 0.59	3.48 (1.51,8.03) <0.001

OR=age-adjusted odds ratio

Yeap BB, et al. JCEM 2012; 97: 4030-9

Figure 9. Associations of low T, DHT and E2 with Frailty, Diabetes and CVD

Men who died had lower baseline testosterone and DHT and after allowance for other risk factors, T and DHT were associated with all-cause mortality. Higher DHT was associated with lower IHD mortality and E2 was not associated with either all-cause or IHD mortality. Optimal androgen levels are a biomarker for survival because older men with midrange levels of T and DHT had the lowest death rates from any cause, whereas those with higher DHT had lower IHD mortality.

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SESSION V: NEW DELIVERY METHODS

Novel Approaches for the Delivery of Testosterone

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Testosterone and other androgens are currently available in oral, nasal, transbuccal, injectable, implants, and transdermal formulated products. The oral formulations such as micronized testosterone is metabolized very rapidly by liver and cannot be used for testosterone replacement therapy. The 17 alkylated androgens (e.g. methyl testosterone, fluoxymesterone) can be absorbed orally but may cause hepatic toxicity and reduction of HDL-cholesterol and increase in LDL-cholesterol levels and thus are not recommended for use as androgen replacement. Testosterone undecanoate (Andriol) is an ester of testosterone that is absorbed orally and has been available for over ten years in Europe, Asia and Canada and used as androgen replacement therapy primarily for the treatment of male hypogonadism. It's adsorption through portal and lymphatic depends on meals and shows large within and between subject variations and is given twice or three times a day at 80 mg BID/TID.[1]

Testosterone Pellets are not commonly used in the US but popular in Australia and Europe in form of 75 mg pellets. It requires surgical implantation using a trocar and four 200mg pellets last about 4 to 5 months. Transdermal testosterone products are available in Patches, Gels, and Lotions preparations. Androderm that is formulated to delivers 5 mg testosterone per day by applying one or two patches can achieved the diurnal variation of normal serum testosterone levels. The testosterone Gel (Androgel/Testogel) (Testim) is formulated in 2.5-5 g gel delivering approximately 2.5 or 5 mg testosterone. It is applied at usual doses of 5 to 10 g per day and show minimal skin irritability unlike skin patches and flexibility of dosing while achieving steady state serum levels (Figure 10).[2]

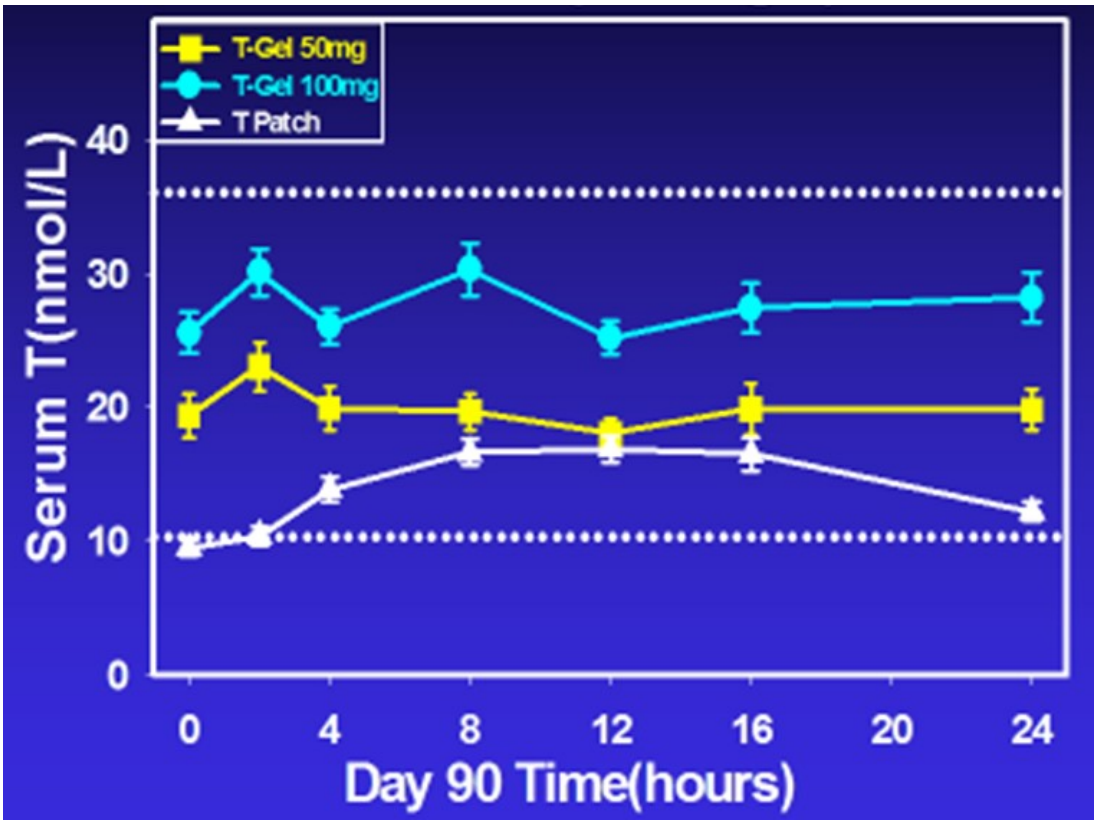

Figure 10. Serum Testosterone Levels on Day 90 after Daily Application of 1% Transdermal Testosterone (Androgel)

Also the Intra-Nasal testosterone gel such as Natesto has been approved by FDA. Natesto nasal gel is available as a metered-dose pump and each pump actuation delivers 5.5 mg of testosterone. It is used twice daily by intranasal application and has the advantage of no portal first pass effect. The injectable testosterone products such as testosterone enanthate or cypionate are intermediate acting products and injected into the muscle at 200 mg/2 weeks or 100 mg/week. Serum testosterone levels increase to supra-physiological levels on days 1 to 3 after injection and fluctuations in serum testosterone levels may result in variations in mood, increased acne and RBC mass. Long Acting Injectable Testosterone products such as Testosterone Undecanoate has large market share in Europe and has the advantages of longer lasting than intermediate acting ones and provide less peaks to valleys ratio.[3]

Beside using testosterone products ad new formulations, other alternative testosterone stimulating drugs has been investigated for male hypogonadism such as hCG, DHT, Selective Androgen Receptor Modulators (SERMs): Clomifene citrate, enclomifene (Androxal), Aromatase Inhibitors (Anastrozole, BGS649 -Novartis) and estrogens receptor blockers (Tamoxifen).[4,5,6]

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SESSION VI: CURRENT CONTROVERSIES -III- COMPLICATIONS OF TRT

Use of TRT in men with LOH: A Precautionary Tale

Abraham Morgentaler, MD, FACS
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Dr Morgentaler provided an overview of overselling testosterone dangerously. He mentioned lots of our attitude toward testosterone is either philosophical or opinion. 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 entitled "Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels".[1] 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.[2] Within a couple of days, FDA announced that is going to review the safety issues and CV risk of using testosterone and the New York Times published an editorial opinion pages entitled "Overselling Testosterone, Dangerously", with the comments that men who get testosterone prescription embarking on a dangerous journey.

The evidences published by Finkle et al article need to be examined carefully as the first author and several co-authors were owner and employment of a company who had access to large database of insurance data and were able to evaluate 55,593 patients who received testosterone prescription. There was only insurance claims data based on diagnosis codes of prescription with no clinical information such as smoking, obesity, and lab results. They compared rates of non-fatal MI 12 months prior to testosterone prescription vs up to 90 days after testosterone prescription (until 1st refill).[2]

The entire study design makes no sense, as pre and post prescription periods are unrelated and this was not an experimental study by design and the pre- and post-testosterone administration periods had no relationship to each other and the comparison was meaningless. The MI rates that was reported as 4.75 MI/1000 person-years with the NIH Heart Attack Risk Calculator that was 13 MI/1000 person-years and that MI rate was low and a fraction of expected rate. The MI rate differences were also not clinically significant as Pre-Rx rate was 3.48 events/1000 person-years and Post-Rx rate was 4.75 events/1000 person-years. The difference was 1.27 events/1000 person-years, which is only one excess event per 1000 person-years of exposure, which is like one more MI in 100 generations of a family. Therefore there was no increased risk of MI following testosterone therapy and a more accurate title of the article should have been like "Physicians Unlikely to Prescribe Testosterone within 12 Months Following MI".

Also the evidences of published article by Vigen et al in JAMA in 2013 is poor and need to be examined carefully. [1] The authors looked at 7486 patients not receiving testosterone therapy and found 681 died, 420 had MIs, and 486 had strokes. Among 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes. The absolute rate of events was claimed to be 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group. Using the same data, Dr. Morgentaler's calculations indicated that absolute rate of events is in fact should have been reported 21.2% (1587/7486) for un-treated and 10.1% (123/1223) for testosterone-treated group. After communicating this to the editor of JAMA, the authors came up with new rates after statistical modelling and excluded 1132 men who received testosterone therapy after MI or stroke. The question is credibility of data and many world's experts petition JAMA (signed by 29 medical societies, >160 distinguished researchers/clinicians, >60 full professors, 8 emeritus, 9 journal editors, 32 countries) to retract testosterone study. Many studies in patients with coronary disease confirmed, those with normal levels of bioavailable testosterone had a significantly longer survival than those with lower levels of bioavailable testosterone (Figure 11).[4]

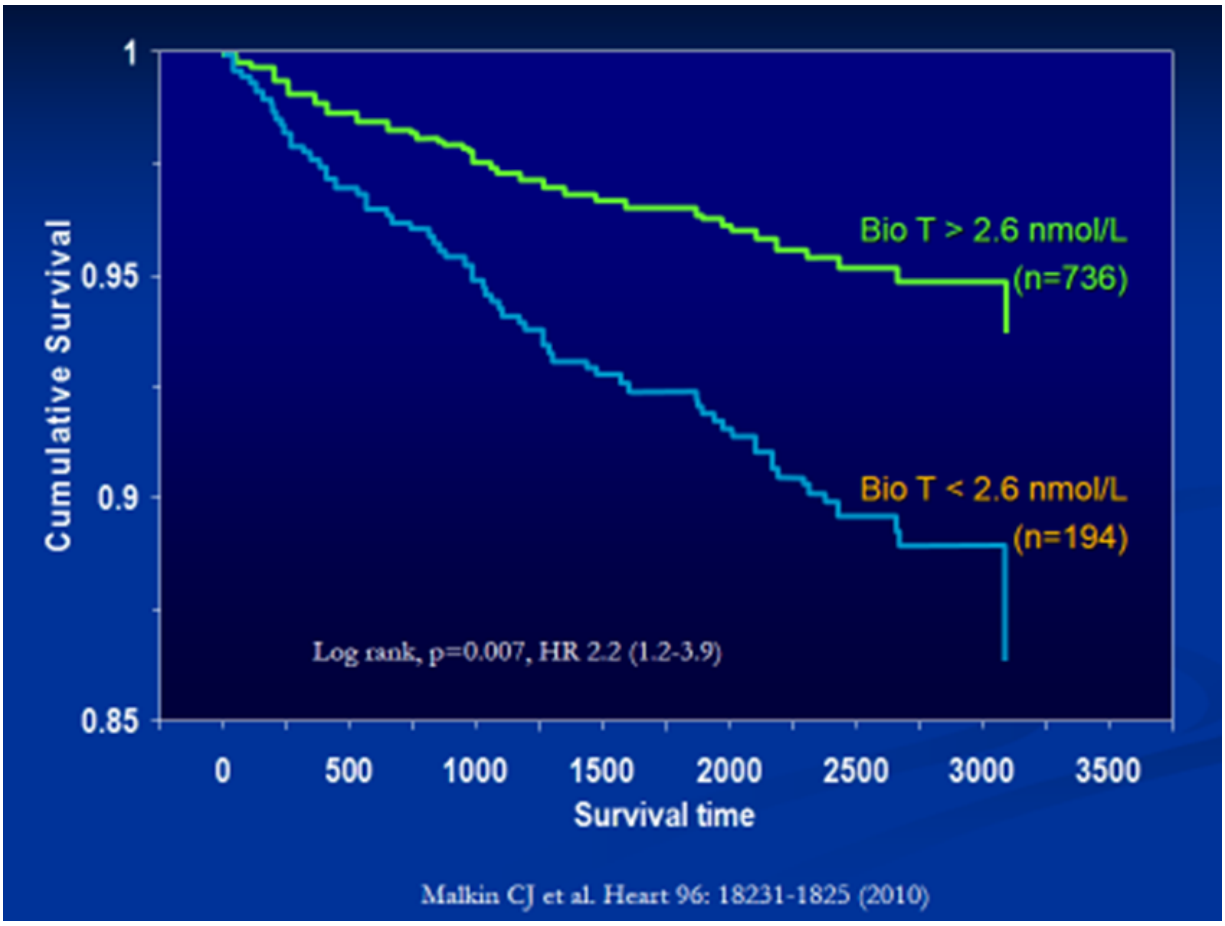

Figure 11. CUMULATIVE SURVIVAL BASED ON BIOAVAILABLE TESTOSTERONE FOLLOWED FOR 6.9 ± 2.6 Y MORTALITY: LOW T 21%, NORMAL T 12%

In summary, the weight of scientific evidence does not support increased CV risks with testosterone therapy and both FDA and European Medicines Agency confirms no increased risk as supported by many literature highlighting the beneficial CV effects of testosterone and increased mortality in men with low testosterone levels. These controversial claims are usually promoted by those who are not involved in the care of men with testosterone deficiency such as anti-pharma advocates, media, plaintiff attorneys, and anti-sex groups.

TRT in Ageing Men: A Potentially Dangerous Cult

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In introduction, Dr Nissen addressed why many in the medical community are up in arms about testosterone treatment. He mentioned that testosterone usage is out of control, driven by scumbag operators running "Low T Centers" and diabolical DTC advertising advocating inappropriate treatment. He mentioned that the biological effects of testosterone are widespread affecting many organ systems and the effects of testosterone treatment on CV outcomes are poorly studied and appear worrisome. The application of testosterone has increased more than 3 folds in the past decade (Figure 12)[5] and if these agents are likely to be harmful, the public health consequences will be truly catastrophic.

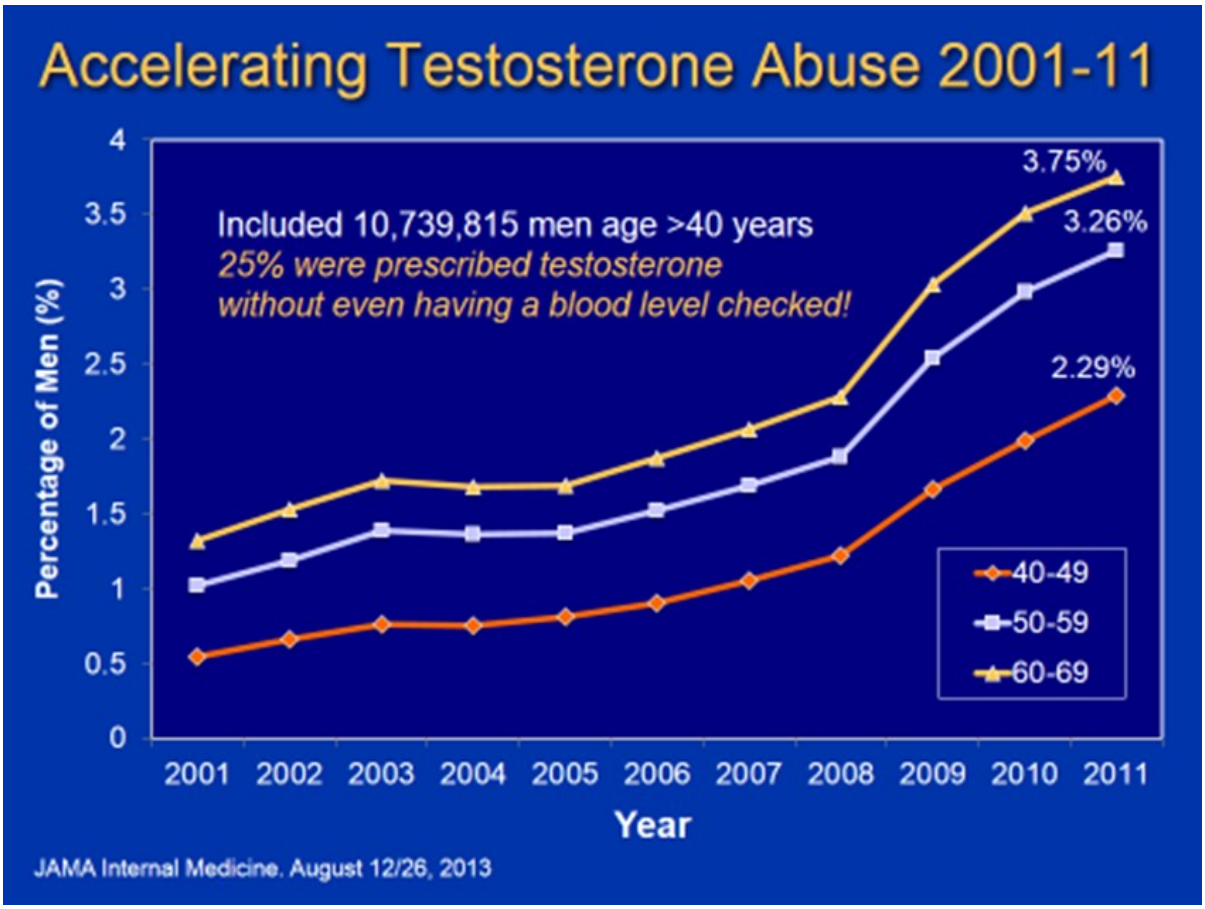

Figure 12. Trends in androgen prescribing in the United States, 2001 to 2011

Dr Nissen then provided an overview of what the science show about the testosterone beneficial effects as the effects are mixed and there are unclear relationship between blood levels and symptoms, more of the biomarkers interest. Few, if any, high quality randomized, controlled cardiovascular outcome trials has been conducted.

In 2010 TOM (Testosterone in Older Men) trial, an small randomized trial (n=209) of the effect of testosterone treatment on leg strength in men (age >65) with mobility limitations and low serum testosterone, the DSMB recommended early trial termination for a significantly higher rate of serious adverse cardiovascular events in the testosterone group.[6]

The existing trials and meta-analyses are worrisome, despite extreme publication bias and large observational studies confirm CV risk. The published article by Vigen et al in JAMA in 2013 found at 3 years after coronary angiography, the Kaplan-Meier estimated cumulative percentages with events were 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group, with an absolute risk difference of 5.8%.[1] The second large retrospective cohort study by Finkle et al in 55,593 patients who received testosterone prescription, the rate ratio for TT prescription increased with age from 0.95 for men under age 55 years to 3.43 for those aged >/= 75 years.[2]

In conclusion, Dr Nissen mentioned that allowing widespread use of testosterone preparations for millions of men with disreputable entrepreneurs leading the charge, fueled by misleading DTC advertising, without an adequate cardiovascular outcome trial is shear folly. The available data suggest favorable effects on surrogate biomarkers, but a strong likelihood of morbid-mortal adverse cardiovascular effects.

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