

Journal für

Reproduktionsmedizin und Endokrinologie

– Journal of Reproductive Medicine and Endocrinology –

Andrologie • Embryologie & Biologie • Endokrinologie • Ethik & Recht • Genetik
Gynäkologie • Kontrazeption • Psychosomatik • Reproduktionsmedizin • Urologie



**4th International Symposium on Testosterone: Action
Deficiency, Substitution - October 1-4, 2011, Schloss
Hohenkammer, Bavaria - Abstracts**

J. Reproduktionsmed. Endokrinol 2011; 8 (3), 201-208

www.kup.at/repromedizin

Online-Datenbank mit Autoren- und Stichwortsuche

Offizielles Organ: AGRBM, BRZ, DVR, DGA, DGGEF, DGRM, D-I-R, EFA, OEGRM, SRBM/DGE

Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz



ENDO FERTI FORUM

ENDOKRINOLOGIE & FERTILITÄT
FÜR KLINIK & PRAXIS

20.-21. März 2026

Universitätsmedizin Mainz

Einladung zu unserer wissenschaftlichen Veranstaltung Endo-Ferti-Forum

Brücke(n) zwischen Unikliniken und Praxen an Rhein und Main(z)

– die aus dem bisherigen Format „Ferti Forum“ ab 2026 hervorgeht –



Freuen Sie sich auf spannende Vorträge und den lebendigen Austausch mit Kolleg:innen und Expert:innen aus Klinik und Praxis. Freitagabend laden wir Sie herzlich zu einem entspannten Empfang ein – eine perfekte Gelegenheit, Kontakte zu knüpfen und den Tag genussvoll ausklingen zu lassen.

Wissenschaftliche Leitung: Univ.-Professorin Annette Hasenburg, Dr. Susanne Theis, Universitätsmedizin Mainz, Sanitätsrat Dr. Werner Harlfinger, BVF Rheinland-Pfalz Dr. Rüdiger Gaase, BVF Hessen Dr. Klaus J. Doubek

Schirmherrschaften: Prof. Nicole Sänger, Uniklinik Bonn, Prof. Jan-Steffen Krüssel, Uniklinik Düsseldorf, Dr. Annette Bachmann, Uniklinik Frankfurt am Main, Prof. Christine Skala, Uniklinik Köln

Weitere Informationen
& Anmeldung unter



4th International Symposium on Testosterone: Action, Deficiency, Substitution

October 1–4, 2011, Schloss Hohenkammer, Bavaria

Abstracts*

A01

Genetic Determinants of Serum Testosterone Concentrations in Men

C. Ohlsson¹, CHARGE Consortium Sex Hormone Working Group¹, R. Haring²

¹Center for Bone and Arthritis Research, Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; ²Institute of Clinical Chemistry and Laboratory Medicine, University of Greifswald, Germany

Introduction Testosterone concentrations in men are associated with cardiovascular morbidity, osteoporosis, and mortality and affected by age, smoking, and obesity. Because of its high heritability, we investigated the genetic determinants of testosterone concentrations in men.

Methods We performed a genome-wide association study of testosterone concentration among 14,429 Caucasian men from 10 cohorts. Seven cohorts were designated discovery cohorts ($n = 8,938$), one in silico replication cohort ($n = 871$), and two de novo replication cohorts ($n = 4,620$). Inverse variance weighted fixed-effect model meta-analysis of study-specific results was performed. Serum testosterone < 300 ng/dl was deemed low.

Results Two independent variants at the sex hormone-binding globulin (SHBG) locus (17p13-p12) reached genome-wide significance in the discovery cohorts and were confirmed in the replication cohorts (combined p -value rs12150660, $p = 1.2 \times 10^{-41}$; rs6258, $p = 2.3 \times 10^{-22}$). Subjects with ≥ 3 risk alleles of these variants had 6.5-fold higher risk of having low serum testosterone than subjects with no risk allele. The rs5934505 polymorphism near FAM9B on the X chromosome was associated with total testosterone ($p = 5.6 \times 10^{-16}$) and free testosterone ($p = 6.7 \times 10^{-15}$) concentrations. The rs6258 polymorphism in exon 4 of SHBG affected SHBG's affinity for testosterone binding and the free testosterone fraction ($p < 0.01$).

Conclusion Genetic variants in the SHBG locus and on the X chromosome are associ-

ated with a substantial variation in testosterone concentrations and increased risk of low testosterone. rs6258 is the first reported SHBG polymorphism, which affects testosterone binding to SHBG and the free testosterone fraction and could influence the calculation of free testosterone using law-of-mass-action equation.

A02

The Content of Five Sex Steroids in Human Testis

J. Heracek^{1,2,3}, R. Hamp⁴, V. Sobotka^{1,2,5}, L. Zamrazilova⁴, L. Sosvorova⁴, M. Urban^{1,2,3}

¹Department of Urology, ^{3d} Faculty of Medicine, Charles University; ²Department of Urology, Teaching Hospital Kralovske Vinohrady; ³Androgeos; ⁴Institute of Endocrinology; ⁵Sanatorium Pronatal; Prague, Czech Republic

Introduction In order to assess whether intratesticular hormone content may be helpful for prediction of successful conception in men with fertility problems.

Objectives The determination of 5 sex steroids in samples of testicular tissues from non-obstructive azoospermic men.

Methods Tissue was obtained from 84 non-obstructive azoospermic men aged 21–67 years (mean $\pm$ SEM: 35.4 ± 9.9) by surgical retrieval. Patients underwent microsurgical testicular sperm extraction (M-TESE) using optical 20–25 $\times$ magnification. The material was immediately frozen in dry carbon dioxide and stored frozen at -70°C until processed. The amounts of tissue varied from 2 to 65 mg. Steroids after ether extraction and solvent partition were separated by high performance liquid chromatography and then measured by specific radioimmunoassays.

Results The values varied considerably with means $\pm$ SD (nmol/g): 2.43 ± 2.47 ; 0.27 ± 0.24 ; 0.080 ± 0.13 ; 0.071 ± 0.0089 and 0.31 ± 0.27 for testosterone, dihydrotestosterone, androstenedione, estradiol and epitestosterone, respectively. The concentrations of testosterone are lower than those reported by early studies which did not use chromatographic separation of the ether extract but agree well with more recent ones. The values of estradiol and androstenedione are comparable with previous findings [Levalle et al., 1994; Takahashi et al., 1982]. We have found higher intratesticular concentrations

of dihydrotestosterone but the groups of subjects in other reports were much smaller.

Conclusions For the first time the values are provided for all steroids of interest in one sample, namely testosterone, its precursor androstenedione and 5 α -reduced metabolite dihydrotestosterone, together with estradiol and epitestosterone. The number of samples and their heterogeneity do not allow statistical evaluation of the relation to the patient's state, especially the sperm parameters, but the method is satisfactory for use in a larger number of samples.

(Grant support: Internal Grant Agency of the Ministry of Health, No. NS9967)

A03

The Concept of Androgen Resistance in the Testosterone Deficiency Syndrome

M. Carruthers

Centre for Men's Health, London, UK

Introduction Central to the diagnosis and treatment of testosterone deficiency syndrome in the adult male is the remarkable paradox that there is very poor correlation between the characteristic symptoms and levels of serum androgens. The aim is to present an evidence-based working hypothesis to resolve this confusing clinical paradox.

Methods A review of the possible mechanisms in testosterone deficiency syndrome was carried out and a hypothesis to explain this paradox and associated problems in the diagnosis and clinical management of androgen deficiency established on the basis of a review of the literature. Mechanisms by which androgen deficiency could arise were studied at five different levels:

1. Impaired androgen synthesis or regulation
2. Increased androgen binding
3. Reduced tissue responsiveness
4. Decreased androgen receptor activity
5. Impaired transcription and translation.

Results As with insulin in maturity onset diabetes mellitus, there can be both insufficient production, and variable degrees of resistance to the action of androgens operating at several levels in the body simultaneously, with these factors becoming progressively worse with aging, adverse life-style, other

* Index of authors (only primary authors) see page 208

disease processes, and diverse medications. Just as insulin resistance is thought to vary between tissues, so is androgen resistance, and therefore, different organs may respond functionally or metabolically with differing consequences. Lifestyle factors in metabolic syndrome and alcohol excess cause fibrosis and damage to both pancreatic islets and Leydig cells, and can be modified with benefit to both conditions. Like diabetes, there can be genetic predispositions to androgen deficiency, both racial and familial, together with variations in CAG and GGN receptors. Temperature, trauma, stress, diet, zenoestrogens, and antiandrogens, can also impair testicular function. Finally, variable transcription, translation and post-translational factors regulate the final steps in androgen action.

Conclusions Using this model, androgen deficiency can be redefined as an absolute or relative deficiency of androgens or their metabolites according to the needs of that individual at that time in his life. There are important ways in which the considerations raised by this hypothesis affect the aetiology, terminology, diagnosis and treatment of androgen deficient states.

A04

Frequent Androgen Deficiency Leading to Abnormal Lipid Profile in Infertile Men with Non-Obstructive Azoospermia

J. Bobjer^{1,2}, M. Naumovska¹, Y. L. Giwercman², A. Giwercman^{1,2}

¹Reproductive Medicine Center, Skåne University Hospital Malmö; ²Reproductive Genetic Research Group, Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden

Introduction In men with non-obstructive azoospermia (NOA), little attention has been paid to the risk of androgen deficiency. Apart from a possible aetiological link between NOA and male hypogonadism, testicular sperm extraction (TESE), which is included in the management of these patients, may further aggravate Leydig cell dysfunction. Hypogonadism may subsequently lead to the development of metabolic syndrome, diabetes mellitus type 2 and cardiovascular disease. Our study aimed to elucidate the prevalence of hypogonadism in NOA patients and to investigate the impact of TESE on the hormone balance as well as the association between testosterone deficiency and unfavourable lipid profile.

Material and Methods Fasting morning blood samples of testosterone, luteinising hormone (LH), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were obtained from 65 NOA-patients (mean age 36 years), who had undergone TESE on average 2.2 ± 1.6 years prior to blood sampling. For 45 of the NOA-patients, pre-TESE morning hormone values

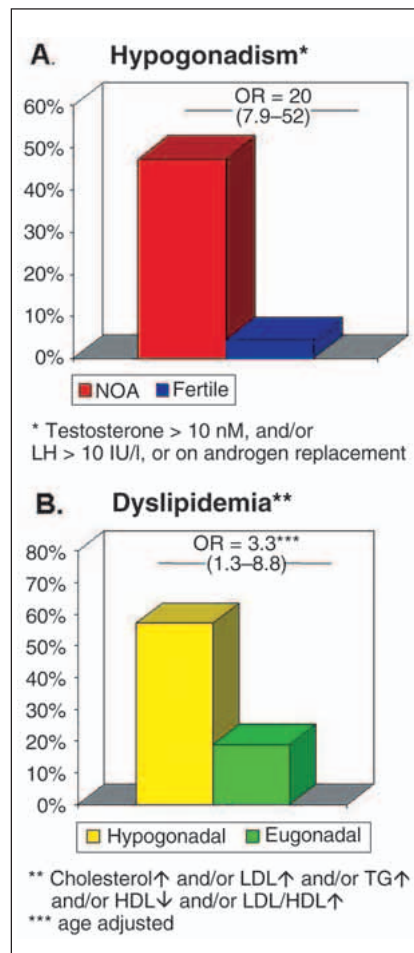


Figure 1. J. Bobjer et al. (A04). **A:** OR for hypogonadism in NOA-men compared to fertile controls. **B:** OR for dyslipidemia in hypogonadal NOA-men compared to eugonadal NOA-men. OR = odds ratio (95% CI).

were also available. Hormone levels were compared with those in 141 proven fertile controls as well as with pre-TESE hormone values. Hypogonadism was defined as serum testosterone ≤ 10 nmol/L and/or serum LH ≥ 10 IU/L and/or ongoing androgen replacement therapy (ART). In addition, testosterone levels were analysed in relation to testicular volume and serum lipids.

Results Hypogonadism was found in 47% of NOA-men (**Fig. 1A**). The post-TESE odds ratio for hypogonadism was 20 (95% CI 7.9–52) as compared to fertile controls. NOA-subjects had significantly higher LH levels ($p < 0.001$) and lower testosterone levels ($p = 0.009$) than fertile subjects. Pre- and post-TESE LH concentrations differed significantly ($p = 0.03$), but testosterone levels did not ($p = 0.43$). Testosterone levels correlated positively with total testicular volume ($p = 0.04$). The OR of having one or more deviations in lipid profile was 3.3 (95% CI 1.3–8.8) for hypogonadal compared to eugonadal NOA-men (**Fig. 1B**).

Conclusions Men with NOA are at very high risk of androgen deficiency, which,

even in young subjects, can be associated with dyslipidemia. Medical management of these men should therefore include endocrinological evaluation and follow up after completion of infertility treatment.

A05

Growing Old Out of Proportions: A Case Report of Kallmann Syndrome

C. R. O. Antonio, J. Montalbo
Department of Internal Medicine, University of the East Ramon Magsaysay Memorial Medical Center, Quezon City, Philippines

Introduction Kallmann Syndrome (KS) is a rare form of congenital hypogonadotropic hypogonadism associated with anosmia or hyposmia, involving 1 out of 10,000 males and even five times lower among females. It is first described in 1856 by a Spanish pathologist and was given genetic etiologic description by Kallmann et al., in 1994. A 28 year old male consulted at Out-Patient Department of our institution with complaints of bilateral knee pain, gait instability and continuous linear growth. Detailed history revealed decreased libido and inability to ejaculate. Physical findings showed a high-pitched voice, eunuchoid habitus, gynecomastia, fat distribution more on chest and hip area, scanty axillary and pubic hair (Tanner Stage II), small descended testes and micropenis. Neurologic examination demonstrated normal findings except for inability to smell and identify test substances (anosmia). Ishihara test for color perception was normal. A form of androgen deficiency was suspect and detailed investigation was performed.

Materials and Methods Laboratory tests were performed to substantiate the investigation. Bone scan, serum total testosterone and serum pituitary panel was done. Echocardiography and kidney ultrasound was also performed to rule out midline defect and other possibility of associated congenital anomalies. Cranial MRI was also done to investigate the pituitary gland and other related structures.

Results Bone scan revealed incomplete closure of the epiphyseal plates, with bone age compatible that of a 15-year old male. Echocardiography and kidney ultrasound revealed normal findings. Total testosterone levels were noted to be low, as well as the level of Luteinizing Hormone and Follicle Stimulating Hormone. Other pituitary hormone levels were noted to be normal. Cranial MRI revealed borderline low volume of pituitary gland and hypoplastic olfactory sulci with non-visualized olfactory bulb.

Conclusion The above findings showed a condition of a secondary hypogonadotropic hypogonadism. Imaging findings showed undeveloped olfactory bulb compatible with Kallmann's syndrome.

A06

Lower Serum Testosterone (T) and Estradiol (E₂) in Adult Men with Unfused Epiphyses Due to Unrecognized and Untreated Congenital Hypogonadotropic Hypogonadism (HH): Evidence for an E₂-Threshold for Bone Maturation in Men

V. Rochira¹, A. Balestrieri², L. Zirilli¹, B. Madeo¹, I. Sgarbi¹, A. Luberto¹, C. Carani¹

¹Chair and Unit of Endocrinology & Metabolism, ²Unit of Endocrinology, Bufalini Hospital, Cesena, Italy

Introduction At puberty, the rise of serum estradiol (E₂) [coming from conversion of testosterone (T)] is needed to fuse epiphyses and to complete bone maturation in normal boys. Due to severe hypogonadism and very low circulating T, adult men with congenital Hypogonadotropic Hypogonadism (HH) may present with unfused epiphyses and continuing linear growth if androgen deficiency is unrecognized and untreated. In order to establish the minimal amount of sex steroids needed to ensure bone maturation we prospectively studied 28 caucasian men first diagnosed as HH in adulthood (a very rare clinical condition).

Material and Methods We prospectively enrolled 28 HH men attending the Unit of Endocrinology from January 1997 to December 2011 and we compared 11 adult HH men (mean age $\pm$ SD: 22.7 $\pm$ 6.1) with fused epiphyses to 17 adult HH men (mean age $\pm$ SD: 21.8 $\pm$ 4.3) with unfused epiphyses.

Serum T, E₂, LH, and FSH were assayed. Bone age, target height, Tanner stage, anthropometrical measurements (height, arm span, upper [U] and lower [L] segments) and bitesticular volume were calculated (Fig. 2). Serum estradiol was detected employing a commercially available double antibody RIA (Third-Generation DSL-39100, Diagnostic System Laboratories, Inc., Webster, TX). Sensitivity was 0.6 pg/ml (2.2 pmol/l) with the lowest standard at 1.5 pg/ml, linearity to 150 pg/ml, and an ED50 of 20 pg/ml. The cross-reactivity with estrone and with less potent estrogens was less than 7 and 0.45%, respectively. The inter-assay and the intra-assay coefficients of variation for estradiol were 4.1–9.9 and 3.4–3.9%, respectively.

Results Bone age, T, E₂, Tanner stage, bitesticular volume were significantly lower in HH men with unfused than with fused epiphyses ($p < 0.001$) (Fig. 2). Height, arm span, the arm span/height ratio, the U/L segment ratio and the difference between patient's height and his calculated target height were significantly greater in HH men with unfused than with fused epiphyses ($p < 0.001$) (Fig. 2). All patients with unfused epiphyses had E₂ < 15 pg/ml and all patients with fused epiphyses had E₂ > 20 pg/ml, while T resulted partially overlapped in the two groups.

Conclusions A threshold of 20 pg/ml exists for serum E₂ above which epiphyseal closure and bone maturation may be reached in men. Setting this threshold is challenging for targeting some kind of treatment for short or tall stature in boys, like aromatase inhibitors or androgens, respectively. Unfused epiphyses, tall stature and eunuchoid skeleton all depend on circulating estrogens rather than androgens not only in genetic diseases due to congenital estrogen deficiency.

A07

Sex-Hormone Trajectories and Their Association With Clinical Cardiovascular Disease and All-Cause Mortality in Elderly Men from the Framingham Heart Study

R. Haring^{1,4}, Z. Teng², V. Xantakis², A. Coviello^{1,3}, L. Sullivan², S. Bhasin³, J. Murabito⁵, H. Wallaschofski², S. Vasan^{1,5}

¹Preventive Medicine & Epidemiology Section; ²Department of Biostatistics; ³Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, USA; ⁴Institute of Clinical Chemistry and Laboratory Medicine, University of Greifswald, Germany; ⁵National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, USA

Introduction Emerging data suggests that low baseline sex hormone concentrations in men are associated with increased follow-up cardiovascular risk and mortality. But the impact of longitudinal sex hormones trajectories on the observed associations is unknown to date.

Methods We used data from 274 elderly men of the Framingham Heart Study (mean age: 75.4 years) with up to four serial sex hormone measurements (total testosterone [TT],

dehydroepiandrosterone sulfate [DHEAS], follicle stimulating hormone [FSH], luteinizing hormone [LH], and total estradiol [EST]) to perform age- and multivariable-adjusted Cox proportional hazard regression models analyzing baseline sex hormone concentrations and their mean, slope, and variability (categorized into quartiles) associated with incident cardiovascular disease (CVD) and all-cause mortality at the 5-year and 10-year follow-up.

Results We found no association between baseline sex hormone concentrations or their trajectory patterns with incident CVD at the 5-year and 10-year follow-up, respectively. Associations between higher TT concentrations and lower all-cause mortality risk (HR: 0.73; 95% CI: 0.55–0.97) were observed in multivariable-adjusted, but not in age-adjusted (HR: 0.81; 95% CI: 0.62–1.06) models. Furthermore, a less steep decline in TT concentrations over the 5-year follow-up was inversely associated with all-cause mortality risk (HR: 0.74; 95% CI: 0.56–0.99) in age-adjusted, but not in multivariable-adjusted models (HR: 0.75; 95% CI: 0.55–1.01). Repeated analyses at the 10-year follow-up confirmed none of the revealed findings.

Conclusion Investigating serial sex hormone measurements and their longitudinal trajectory patterns, the present study found no consistent associations with incident CVD and all-cause mortality risk.

A08

Mendelian Randomization Suggests Non-Causal Associations of Testosterone with Cardiometabolic Risk Factors and Mortality: Results from the Study of Health in Pomerania

R. Haring¹, A. Teumer², U. Völker², M. Dör³, M. Nauck¹, R. Biffar⁴, H. Völzke⁵, S. E. Baumeister^{5*}, H. Wallaschofski^{1*} (* both authors contributed equally)

¹Institute of Clinical Chemistry and Laboratory Medicine; ²Department of Functional Genomics; ³Department of Cardiology; ⁴Center of Dentistry and Oral Health; ⁵Institute for Community Medicine, University of Greifswald, Germany

Introduction Recent findings from prospective studies suggest that low serum testosterone concentrations are associated with

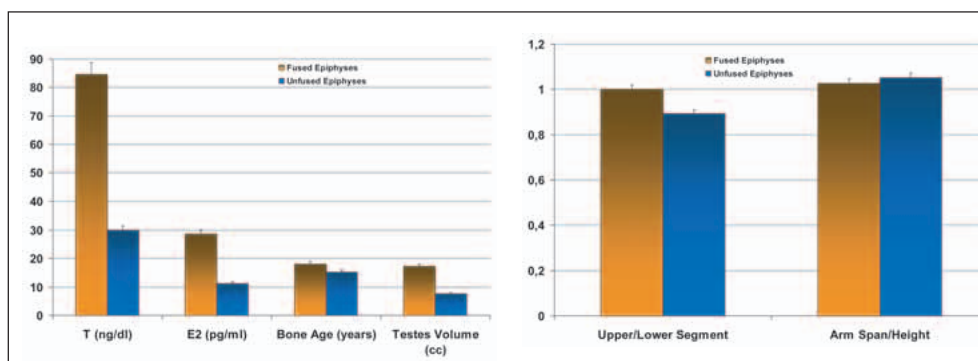


Figure 2. V. Rochira et al. (A 06). Sex steroids, bone age, bitesticular volume, and anthropometry in HH men with fused and unfused epiphyses.

various cardiometabolic risk factors and mortality. But the causal nature of these associations is controversial.

Methods We studied 1,882 men with serum testosterone concentrations and genotyping data from the population-based Study of Health in Pomerania. We used two previously identified polymorphisms at the SHBG gene, which significantly influence serum testosterone concentrations and applied an instrumental variable approach with genetic instruments (also known as Mendelian randomisation) to overcome problems of reverse causation, confounding, or regression dilution bias in the testosterone-outcome associations.

Results In standard regression analyses, serum testosterone was significantly associated with a wide range of cardiometabolic risk factors. In subsequent instrumental variable regression analyses using the SHBG variants rs12150660, rs6258, and their combination, no such associations were observed. Similarly, Poisson regression models showed a consistent association of low serum testosterone concentrations with increased all-cause mortality risk, which was not apparent in subsequent instrumental variable Poisson models.

Conclusion As Mendelian randomization did not detect any evidence for causal associations of serum testosterone concentrations with cardiometabolic risk factors and mortality, previously reported associations might largely result from confounding, reverse causation, or regression dilution bias. Rather than as a causal precursor, testosterone assessment may play a role as an intermediate or surrogate marker of subclinical disease progression.

A09

Clinical Correlates of Sex Hormone Concentrations in Men Over the Adult Life Course: the Framingham Heart Study

R. Haring^{1,4}, I. Xanthakis², A. Coviello^{1,3}, L. Sullivan², S. Bhasin³, H. Wallaschofski⁴, J. M. Murabito^{1,5}, R. S. Vasan^{1,5}

¹Preventive Medicine & Epidemiology Section and Section of General Internal Medicine; ²Department of Biostatistics; ³Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, USA; ⁴Institute of Clinical Chemistry and Laboratory Medicine, University of Greifswald, Germany; ⁵National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, USA

Introduction Low sex hormone concentrations in men have been associated with increased cardiometabolic risk and mortality, but the clinical correlates of sex hormone concentrations in men over the adult life course are less clearly understood.

Methods We analyzed up to 5 serial sex hormone measurements (total testosterone [TT], dehydroepiandrosterone sulfate [DHEAS], follicle stimulating hormone [FSH], luteinizing hormone [LH], and total estradiol [EST])

in older men in the original cohort of the Framingham Heart Study to determine the short- (2-years; 1,165 person-observations in 528 individuals) and long-term (up to 10-years follow-up; 2,520 person-observations in 835 individuals with mean age: 71.2 years) clinical correlates of these hormones using multilevel modeling and Generalized Estimating Equations.

Results Age, body mass index, and prevalent type 2 diabetes were inversely related to long-term TT concentrations, whereas higher systolic blood pressure showed a positive association. Furthermore, age and prevalent cardiovascular disease (CVD) were inversely and HDL cholesterol concentrations positively associated with long-term DHEAS concentrations. Analyses of short-term changes revealed age inversely related to DHEAS, but positively related to FSH and LH concentrations. Overall, men with an optimal CVD risk factor profile maintained higher TT and DHEAS concentrations over the 10-year period.

Conclusion Our community-based longitudinal study identified modifiable correlates of decreasing TT and DHEAS concentrations over the life course of elderly men, suggesting that maintenance of an optimal risk factor profile may mitigate the age-related decline in levels of these hormones.

A10

Continuous Improvements of Features of the Metabolic Syndrome over 48 Months Upon Normalization of Serum Testosterone in 2 Cohorts of Men

J. G. Gooren¹, A. Haider², A. Yassin³, F. Saad⁴

¹Department of Endocrinology, VUmc, Amsterdam, The Netherlands; ²Private Urology Praxis, Bremerhaven, Germany; ³Institute for Andrology and Urology, and Segeberger Kliniken, Norderstedt, Germany; ⁴Bayer Pharma, Scientific Affairs Men's Healthcare, Berlin, Germany and Gulf Medical University School of Medicine, Ajman, UAE

Introduction Men > 40 years often show a concurrence of a decline of testosterone with features of the metabolic syndrome. This study tested the effects of normalization of testosterone over a period of 48 months in two cohorts of men, studied in two clinics, following the same treatment protocol.

Subjects and Methods Cohort AH: 104 men aged 34–78 years (mean $\pm$ SD: 62 $\pm$ 8 yrs) with baseline testosterone 5.9–12.0 nmol/l, and cohort AY: 130 men aged 46–79 years (mean $\pm$ SD: 61 $\pm$ 9 yrs) with baseline testosterone 6.1–12.0 nmol/l were treated with parenteral testosterone undecanoate for 48 months as the sole intervention.

Results Plasma levels of testosterone rose from 9.3 $\pm$ 1.7 to 18.7 $\pm$ 2.1 nmol/l reaching their maximum at 9 months and remaining stable over the next 33 months. Results are presented in tables AH and AY. There was a

remarkable progressive decline of body weight and waist circumference over the full study period, most outspoken over the first 24 months. Plasma cholesterol, triglycerides, and LDL-cholesterol decreased significantly over the study period. Plasma HDL increased significantly over the first 24 months and then declined in cohort AH but increased over 48 months in cohort AY. Plasma glucose declined over the first 12–18 months and then stabilized. Systolic blood pressure declined over 48 months in cohort AH and declined over 24 months to stabilize thereafter in cohort AY. At baseline, 79/104 men in cohort AH and 93/130 men in cohort AY met the criteria of the metabolic syndrome by the harmonized definition. After 48 months of testosterone treatment this number had declined to 50/104 in cohort AH and to 62/130 in cohort AY (Table 1).

Conclusion With testosterone treatment over 48 months, the most significant improvement of variables of the metabolic syndrome was noted over the first 24 months with further improvement over the following 24 months. Body weight and waist circumference declined paralleled by improvements of cholesterol, LDL and triglycerides. A large number of men did not qualify as suffering from the metabolic syndrome after 48 months. Our data originating from two different clinics show a remarkable consistency in results.

A11

Testosterone Substitution Therapy and Prostate: Findings of Transrectal Ultrasound of Prostate in Patients with Primary Hypogonadism

J. Heracek^{1,2,3}, V. Sobotka^{1,2,4}, M. Snajderová⁵, K. El Balouly¹, D. Zemkova⁵, M. Urban^{1,2,3}

¹Department of Urology, ²Faculty of Medicine, Charles University; ³Department of Urology, Teaching Hospital Kralovske Vinohrady; ⁴Androgeos; ⁵Sanatorium Pronatal; ⁶Department of Paediatrics, 2nd Faculty of Medicine, Charles University; Prague, Czech Republic

Introduction Prostate safety is a primary concern in men receiving testosterone replacement therapy (TST). Long-term studies assessing benefits and risks of TST in men indicate that it may produce a wide range of benefits for men with hypogonadism but little information is available regarding its effects on prostate tissue.

Objectives The aim of the study was to assess and evaluate the imaging findings of the prostate over an extended period in patients with primary hypogonadism receiving TST.

Methods 22 patients (aged 18–60 years) were observed since 2002 with different types of primary hypogonadism. TST was performed by continuous therapy (every 4 weeks Sustanon® or every 3 months Nebido® i. m.). The transrectal ultrasonography of prostate and seminal vesicles with 3D reconstruction was evaluated every 6 months.

Table 1: J. G. Gooren et al. (A 10)

		AH					
	Unit	0	12	24	36	48	
Waist circumference	cms	109.1 ± 10	105.5 ± 8.7	103.4 ± 8.7	102.2 ± 8.1	100.9 ± 7.7	
Weight	kgs	107.6 ± 16.2	102.9 ± 14.1	99.1 ± 13.6	97.0 ± 11.9	94.3 ± 11.0	
Glucose	75–110 mg/dl	105.8 ± 18.4	99.8 ± 13.5	96.2 ± 12.0	96.8 ± 8.2	97.0 ± 3.7	
Cholesterol	< 220 mg/dl	297.7 ± 37.7	214.0 ± 33.3	197.4 ± 21.1	198.5 ± 17.0	194.5 ± 14.2	
HDL	< 55 mg/dl	65.5 ± 29.8	68.7 ± 25.1	74.6 ± 28.2	53.3 ± 20.0	52.8 ± 19.2	
LDL	< 150 mg/dl	160.4 ± 42.7	132.5 ± 36.8	121.1 ± 37.8	119.4 ± 34.2	118.3 ± 34.7	
Triglyceride	< 180 mg/dl	290.4 ± 54.6	213.8 ± 41.7	198.9 ± 29.2	196.9 ± 18.0	194.2 ± 16.2	
Systolic BP	mmHg	157.6 ± 15.2	145.7 ± 14.7	142.7 ± 12.0	142.5 ± 11.8	141.4 ± 11.3	
Diastolic BP	mmHg	95.7 ± 11.0	85.4 ± 9.3	83.1 ± 8.4	82.1 ± 7.6	81.9 ± 7.7	
		AY					
	Unit	0	12	24	36	48	
Waist circumference	cms	107.6 ± 9.2	102.0 ± 8.1	100.9 ± 7.8	98.4 ± 7.1	97.4 ± 6.2	
Weight	kgs	106.3 ± 12.8	97.5 ± 16.8	97.6 ± 12.2	94.0 ± 10.6	92.8 ± 9.3	
Glucose	75–110 mg/dl	111.4 ± 33.3	96.7 ± 18.2	100.4 ± 16.1	99.8 ± 14.3	99.0 ± 16.5	
Cholesterol	< 220 mg/dl	268.7 ± 43.0	209.9 ± 28.8	245.9 ± 48.1	224.6 ± 41.0	223.4 ± 46.1	
HDL	< 55 mg/dl	39.2 ± 14.4	49.3 ± 12.3	54.0 ± 17.7	59.3 ± 16.6	56.0 ± 16.7	
LDL	< 150 mg/dl	165.5 ± 23.5	132.7 ± 28.2	140.5 ± 32.6	132.1 ± 38.6	126.0 ± 37.4	
Triglyceride	< 180 mg/dl	262.9 ± 66.7	210.1 ± 41.7	235.8 ± 56.1	217.0 ± 52.1	216.8 ± 44.1	
Systolic BP	mmHg	141.5 ± 13.3	129.4 ± 8.9	125.9 ± 6.6	123.5 ± 4.8	123.2 ± 4.4	
Diastolic BP	mmHg	80.9 ± 10.0	76.8 ± 5.0	79.1 ± 5.5	79.1 ± 2.8	79.0 ± 3.5	

Results We observed progressive prostatic cysts in 9 patients (41%), progressive prostatolithiasis in 11 patients (50%) and progressive hyperechogenic lesion in 5 patients (23%). 2 of these patients (9%) with combined prostatic cyst and prostatolithiasis, and 4 (18%) patients with combined hyperechogenic lesion and prostatolithiasis. Only 3 (14%) patients presented a normal picture of TRUS of prostate.

Conclusions TST has a wide range of benefits, but its safety with regard to the prostate seems to be debatable. Long-term monitoring of these patients in interdisciplinary co-operation between urologists and endocrinologists can help to clarify the impact of testosterone substitution therapy on the development and volume of the prostate.

(Grant support: Internal Grant Agency of the Ministry of Health, No. NS9983)

A12

Prostatic Cyst as a New Finding in Patients with Kallmann Syndrome Treated by Long Term Testosterone Replacement Therapy

J. Heracek^{1,2,3}, V. Sobotka^{1,2,4}, M. Snajderová⁵, K. El Balouly¹, D. Zemkova⁵, M. Urban^{1,2,3}

¹Department of Urology, ²Faculty of Medicine, Charles University; ³Department of Urology, Teaching Hospital Kralovské Vinohrady; ⁴Androgeos; ⁵Sanatorium Pronatal; ⁶Department of Paediatrics, 2nd Faculty of Medicine, Charles University; Prague, Czech Republic

Introduction Kallmann syndrome (KS) is a very rare hereditary disease. KS is a genetic condition characterized by primary hypogo-

nadism and anosmia or hyposmia. Many studies indicate that beside hypogonadism and anosmia, KS clinical presentation is occasionally associated with additional urological features such as renal agenesis/dysgenesis and kidney malrotation, dilatation of the calyces, or agenesis of the spermatic duct, but with no information regarding the prostate of these patients.

Objectives The study objective was long-term monitoring of the prostate in patients with Kallmann syndrome receiving testosterone substitution therapy (TST) by transrectal ultrasound (TRUS) in comparison with changes of the prostatic specific antigen (PSA).

Methods Since 2002, 9 patients (aged 18–32 years) with Kallmann syndrome have received extensive care and follow up in addition, monitoring of the prostate volume and changes by TRUS and PSA examination every 6 months. TST was performed by continuous therapy (every 4 weeks Sustanon® or every 3 months Nebido® i.m.).

Results TRUS proved newly diagnosed prostatic cysts in 6 (67%) patients with no clinical symptoms, 1 (11%) patient with hyperechogenic prostatic lesion, while the PSA results show no significant changes with an average of 0.28 (0.27–0.31) mg/l.

Conclusions This study indicates that prostatic cyst could be a highly possible associated feature in patients with KS. Furthermore special care and monitoring of the prostate in patients with KS are needed to help clarify the impact of TST on development of androgen-dependent organs.

(Grant support: Internal Grant Agency of the Ministry of Health, No. NS9983)

A13

Rationale and Clinical Effect of Cyclic High Dose Testosterone as Therapy For Men With Castration Resistant Prostate Cancer

S. R. Denmeade, J. T. Isaacs

Department of Oncology, The Johns Hopkins University School of Medicine, Baltimore, USA

Introduction In most patients with castration resistant prostate cancer (CRPC), prostate cancer cells continue to express androgen receptor (AR) and continue to grow by AR signaling through adaptation to the > 90% suppression of serum androgen. Second-line hormonal treatments are used to reduce AR signaling by either competitive AR binding antiandrogens or by inhibitors of non-testicular synthesis of testosterone (T). PSA progression in these men documents that, even with combined hormonal therapies, AR is still functioning. Continued AR signaling by CRPCs is the result of a significant increase in AR expression that is sufficient to generate ligand bound AR in the nucleus despite low androgen levels. This AR increase, however, creates a therapeutic vulnerability to selectively kill CRPCs that is based upon the fact that AR is involved in the process of DNA licensing. Based on our studies demonstrating AR binding to origin of replication sites (ORS) during the DNA licensing phase, we documented that AR is degraded via the proteasome during mitosis and rapidly re-synthesized in early-G₁. However, if

AR is not sufficiently degraded in mitosis by CRPCs, these cells do not completely re-license their DNA and die in the next cell cycle.

Methods These preclinical results suggested that significant clinical response could be achieved if progressing CRPC patients were treated with “bipolar androgen therapy” by acute cycling between sequential periods of exposure to supraphysiologic T to further increase and stabilize the enhanced level of nuclear AR to block full relicensing due to insufficient removal of AR from the ORS in mitosis followed by castrate levels of testosterone (T). CRPC cells that survive such acute high androgen replacement via adaptive downregulation of their high AR expression should re-establish vulnerability to apoptosis in this androgen ablated environment. To test this hypothesis, we designed a pilot Phase I trial to test the safety and efficacy of cyclic therapy with high dose parenteral T in castrated men in combination. In addition, based on results demonstrating that T repletion of androgen-depleted cells resulted in DNA double strand breaks (DSBs) mediated through recruitment of AR and topoisomerase II beta (TOP2B) to AREs that could be stabilized with the use of the potent TOP2B inhibitor etoposide (E), men on the trial also received 2 weeks of oral E (100 mg/day) beginning with each T injection. This trial was conducted in men receiving continuous castrating therapy for ≥ 1 year with low levels of metastatic burden. These men remained on castrating therapy and received an intramuscular injection of 400 mg testosterone cypionate once a month for a minimum of 3 months.

Results This regimen was well tolerated with the major side effects being nausea, fatigue and alopecia induced by E. None of the 6 men with low metastatic burden experience worsening of pain or other prostate cancer-related morbidity due to T injection. Supraphysiologic T levels peaked at day 1–2 at > 1000 ng/dl and remained elevated to ~ 700 ng/dl at 2 weeks post injection. However, while serum T approached near-castrate levels at the end of each 28-day cycle, no men achieved true castrate levels. Three of six patients who completed 3 monthly cycles of treatment have experienced a $> 50\%$ overall decline in their PSA levels. One patient experienced a $> 85\%$ PSA response and remains on study after receiving 8 cycles.

Conclusions Injection of high doses of T monthly in combination with E produces supraphysiologic levels of T. However, castrate levels of T are not achieved after one month. The combination is relatively well tolerated and generated PSA declines in 50% of treated men. Future studies will be aimed at achieving true bipolar therapy through addition of antiandrogens and T synthesis inhibitors.

A14

Is Testosterone Treatment Good for the Prostate? Study of Safety during Long-Term Treatment

M. R. Feneley¹, M. Carruthers²

¹Institute of Urology and Nephrology, University College Hospital; ²Centre for Mens Health, London, UK

Introduction For men on testosterone replacement therapy (TRT), clinical concern relates to the development of prostate cancer (PCa). An updated audit of prostate safety from the UK Androgen Study (UKAS) is presented analyzing the incidence of PCa on baseline screening, and during long-term TRT.

Methods 1,365 men aged 28–87 (median 55) years with symptomatic androgen deficiency and receiving TRT have been monitored for up to 20 years. All patients were pre-screened for PCa by digital rectal examination (DRE) and serum PSA, with 6 monthly endocrine, biochemical, hematological and urinary profiles. Abnormal findings or rising PSA were investigated by transrectal ultrasound and prostate biopsy. The data were compared for the 4 different testosterone preparations used, pellet implants, Restandol, mesterolone, and Testogel.

Results 14 new cases of PCa were diagnosed at ages 57–78 years, after 2,966 man-years of treatment (1 case per 212 man-years treatment). Time to diagnosis ranged from 6 months to 12 years (median 5.9 years). All tumours were clinically localized, and suitable for potentially curative treatment. Initiating testosterone treatment had no statistically significant effect on total PSA, free PSA or total/free PSA ratio, and any initial PSA change had no predictive relationship to subsequent diagnosis of cancer.

Conclusions The incidence of PCa in this group of men treated with 4 different testosterone preparations over many years was equivalent to that expected in the general population. This study adds to the considerable weight of evidence that with proper clinical monitoring, testosterone treatment is safe for the prostate, and improves early detection of PCa. By reducing lower urinary tract symptoms, and the diverse structural changes in the urogenital tract caused by hormone deficiency, testosterone treatment may be considered overall to be good for the prostate and safer for the individual than any alternative without surveillance.

A15

Possible Ways Forward in Androgen Treatment

M. Carruthers

Centre for Men's Health, London, UK

Objectives Testosterone deficiency is having an increasing impact on men's health because of global aging, increasing obesity, diabetes and environmental factors and an explanation is needed why so few androgen deficient men are being treated.

Methods Demographic data for men over the age of 50 from different regions of the world have been compared with the number of men in that age group estimated from sales figures to be receiving testosterone treatment.

Results Based on the 20% of men over 50 in the general population who are expected to have testosterone deficiency symptoms, on average only 0.69% of these men in most European countries were receiving treatment. The proportion was higher in the UK (1.00%) and Germany (1.89%), but lower in France (0.49%), Italy (0.51%) and Russia (0.54%). Australia had higher figures (1.64%), in spite of tight state control measures on androgen use. The USA has the highest treatment rate (7.96%) and this is increasing rapidly.

Based on symptoms plus low total and free testosterone levels, androgen deficiency would be diagnosed in at least 5% of men over 50, and percentage treatment rates therefore four times higher. However, even on that basis, only in the USA do these exceed 10%.

Conclusions International action is urgently needed to raise awareness in the medical profession in the various countries of these unacceptably low levels of testosterone treatment. Improvement in this requires education and motivation of doctors and those regulating the healthcare systems.

A16

Testosterone Secretion Profiles Before and After Kidney Transplantation in Adult Males Patients

M. S. Hamdi¹, N. Kamar², L. Bujan¹, R. Miesusset¹, L. Rostaing²

¹Université de Toulouse, UPS, Groupe de Fertilité Humaine (EA 3694, Human Fertility Research Group);

²Department of Nephrology, Dialysis, and Organ Transplantation, CHU Rangueil, Toulouse, France

Introduction Since the restoration of hormonal profiles after successful renal allograft is still controversial, we investigated the change of pituitary hormones and testosterone before and after kidney transplantation in 98 men.

Material and Methods 98 adult males (mean: 47 years) were studied longitudinally while undergoing hemodialysis (median length: 30 months) and six months after kidney transplantation. Pre- and post-operative serum specimens were collected to assess LH, FSH, prolactin and total testosterone levels by an automated immunoassay. 88% of the patients received calcineurin inhibitors and glucocorticoids as immunosuppressors.

Results Just prior to kidney transplantation, median serum levels of LH, FSH, prolactin and the mean level of testosterone were within their reference ranges; however, 29% of the patients were hypergonadotropic (LH and/or FSH), 37% were hyperprolactinemic

and 28% were hypogonadic. Six months after transplantation, the median serum level of LH and prolactin decreased significantly ($p < 0.001$), surprisingly that of FSH showed a significant increase (from 5.1 to 10.6 UI/l; $p < 0.001$). Serum testosterone levels exhibited a non-significant decline ($p < 0.078$); however, more patients were hypogonadic (38%). We thus identified amongst transplanted patients four testosterone secretion profiles: patients who remain eugonadic after transplantation (47%), those who become hypogonadic (21%), patients who remain hypogonadic (15%) and those who normalize their testosterone (11%). Overall, hypogonadic graft recipients presented higher baseline levels of FSH ($p < 0.046$), higher baseline ratio of LH/testosterone ($p < 0.033$) and lower baseline levels of testosterone ($p < 0.001$) than eugonadic ones.

Conclusion Despite an improvement of serum LH and prolactin levels after kidney transplantation, a significant number of patients remained hypogonadic and/or showed elevated serum FSH, suggesting a persisting abnormal pituitary-gonadal axis.

A17

Age-Specific Reference Ranges for Serum Androstenedione and Testosterone Concentrations in Women Measured by Liquid Chromatography-Tandem Mass Spectrometry

R. Haring¹*, A. Hannemann¹*, U. John², D. Radke³, M. Nauck¹, H. Wallaschofski¹, L. Owen⁴, J. Adaway⁴, B. G. Keevil⁴, G. Brabant⁴ (* both authors contributed equally)

¹Institute of Clinical Chemistry and Laboratory Medicine; ²Institute of Epidemiology and Social Medicine;

³Institute for Community Medicine, University of Greifswald, Germany; ⁴Department of Clinical Chemistry, University Hospital South Manchester, UK

Introduction Radioimmunoassay-based sex hormone measurements offer only limited precision and specificity in the low concentration range of women. Therefore, we aimed to establish age-specific reference ranges for serum sex hormone concentrations in women using mass spectrometry and quantile regression.

Methods Data from 1,252 women aged 20–80 years, recruited for the prospective Study of Health in Pomerania (SHIP), were included in the analyses. Quantile regressions models were performed to calculate the age-specific 2.5th and 97.5th percentiles for sex

hormone concentrations in women. Serum total testosterone (TT) and androstenedione (AD) concentrations were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Measured concentrations of sex hormone-binding globulin (SHBG) and TT were used to calculate free testosterone (free T).

Results TT and AD concentrations showed a distinct age-related decline across 10-year age-groups (one-way ANOVA $p < 0.001$). Sex hormone reference ranges for TT, AD, and free T were determined across each single year of age and for 10-year age-groups. Reference ranges over the whole age range of 20–80 years were 0.33–1.89 nmol/l for TT, 0.74–4.58 nmol/l for AD, and 0.0019–0.0223 nmol/l for free T. Separate reference ranges were provided for pre- and postmenopausal women, as well as for women without use of oral contraceptives or hormone therapy.

Conclusion This is the first study to establish age-specific reference ranges for LC-MS/MS-measured TT, AD, and calculated free T concentrations based on quantile regression analyses, accurately accounting for the observed low concentration range and the strong age-dependency of these sex hormones in women.

A18

Pharmacokinetics and Pharmacodynamic Efficacy of Testosterone Intranasal Gel in Women with Hypoactive Sexual Desire Disorder and Anorgasmia

H. Van Gorsel¹, E. Laan², N. Tkachenko³, J. Dickstein³, W. Kreppner³

¹Centre for Human Drug Research, Leiden; ²AMC, Amsterdam, The Netherlands; ³Trimel Pharmaceuticals, Canada

Objective To assess the testosterone and dihydrotestosterone (DHT) pharmacokinetic profile and initial pharmacodynamic efficacy following administration of testosterone intranasal gel (TBS-2), in women with hypoactive sexual desire disorder (HSDD) and anorgasmia.

Method A total of 32 women with HSDD ($n = 16$) and anorgasmia ($n = 16$) were included in this randomized, parallel group, placebo and active comparator study. Women received five doses of TBS-2, placebo TBS-2 (anorgasmia cohort) or a single Intrinsa patch (HSDD cohort) for three consecutive

study days. Frequent sampling pharmacokinetic series were collected after the first dose (0–12 hours) and after the 5th dose (48–60 hours after first dose). Initial pharmacodynamic efficacy was explored using vaginal pulse amplitude (VPA), subjective arousal questionnaires (SAQ, AFSDQ) and validated computer tasks. Safety was monitored throughout the study.

Results The pharmacokinetic results show that there is a linear increase in plasma testosterone levels with increasing dose levels. Mean concentrations of plasma testosterone 0–12 hours after dosing were: 53.38 ng/dl after TBS-2 high dose, 34.55 ng/dl after TBS-2 medium dose and 21.35 ng/dl after TBS-2 low dose. The mean concentration of plasma testosterone is consistently higher after five administrations (48–60 hours post first dose): 65.52 ng/dl after TBS-2 high dose, 44.49 ng/dl after TBS-2 medium dose and 21.81 ng/dl after TBS-2 low dose.

A statistically significant contrast in VPA after 30 minutes is observed in the TBS-2 high dose group compared to placebo in the ANOR cohort (61% difference; $p = 0.04$). After 4.5 hours a statistically significant contrast in VPA is observed in the TBS-2 low dose compared to placebo in the ANOR cohort (82% difference; $p = 0.039$).

A statistically significant increase in sexual arousal was observed in women who received TBS-2 high dose compared to women who received Intrinsa ($p = 0.039$). Women receiving TBS-2 high dose showed a significant increase in sensuality compared to women receiving the Intrinsa patch ($p = 0.032$). Similarly, a statistically significant increase in positive affect was observed between HSDD women receiving TBS-2 high dose and women receiving Intrinsa after 30 minutes and 4.5 hours post dose ($p = 0.034$ and $p = 0.031$ respectively).

No safety concerns were identified in this study.

Conclusions Testosterone intranasal gel (TBS-2) administration resulted in a rapid increase in plasma testosterone levels without exceeding the upper limit of normal thus limiting safety concerns.

This novel intranasal delivery of testosterone induces physiological and subjective sexual arousal in women with anorgasmia and HSDD at both 0.5 hrs and 4.5 hrs. This bimodal response can be explained by direct nose to brain transport of testosterone via nerve projections (the olfactory nerve) along with absorption into systemic circulation.

Index of Authors

(only first authors)

A	F	O
Antonio C. R. O. 202	Feneley M. R. 206	Ohlsson C. 201
B	G	R
Bobjer J. 202	Gooren J. G. 204	Rochira V. 203
C	H	V
Carruthers M. 201, 206	Hamdi M. S. 206	Van Gorsel H. 207
D	Haring R. 203 (2x), 204, 207	
Denmeade S. R. 205	Heracek J. 201, 204, 205	

Mitteilungen aus der Redaktion

Besuchen Sie unsere Rubrik

☒ Medizintechnik-Produkte



Neues CRT-D Implantat
Intica 7 HF-T QP von Biotronik



Artis pheno
Siemens Healthcare Diagnostics GmbH



Philips Azurion:
Innovative Bildgebungslösung

Aspirator 3
Labotect GmbH



InControl 1050
Labotect GmbH

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

☒ Bestellung e-Journal-Abo

Haftungsausschluss

Die in unseren Webseiten publizierten Informationen richten sich **ausschließlich an geprüfte und autorisierte medizinische Berufsgruppen** und entbinden nicht von der ärztlichen Sorgfaltspflicht sowie von einer ausführlichen Patientenaufklärung über therapeutische Optionen und deren Wirkungen bzw. Nebenwirkungen. Die entsprechenden Angaben werden von den Autoren mit der größten Sorgfalt recherchiert und zusammengestellt. Die angegebenen Dosierungen sind im Einzelfall anhand der Fachinformationen zu überprüfen. Weder die Autoren, noch die tragenden Gesellschaften noch der Verlag übernehmen irgendwelche Haftungsansprüche.

Bitte beachten Sie auch diese Seiten:

[Impressum](#)

[Disclaimers & Copyright](#)

[Datenschutzerklärung](#)