EUROPEAN ACADEMY OF ANDROLOGY

Dear EAA Members,

The first summer edition is full of interesting articles – so you can read something during your travels or while on the beach (*just kidding...*). The latest issue of Andrology is based on the North American Testis Workshop, and will be of interest mainly for basic scientists but clinicians will also benefit from several excellent review articles, incl. therapies targeting dysfunctional Leydig cells (*scroll to the end of this alert*). In addition, this alert contains several important articles on testosterone therapy, incl. the first results from the highly awaited TRAVERSE trial; AMH and INSL3 as clinical markers; TRT after TESE; models for hormone treatment of adolescents and trans-boys; exciting news on the Y chromosome and cancer; SART3 variants and gonadal dysgenesis, gene variants linked to high-risk testicular cancer and prostate cancer; a ground-breaking study on the sperm axoneme structure, metabolomics of seminal fluid, and much more.

Clinical andrology and epidemiology

The NEW ENGLAND JOURNAL of MEDICINE

The cardiovascular safety of testosterone-replacement therapy (TRT) in older men has been debated.

This randomised, placebo-controlled trial including 5246 men (45-80 years of age), with hypogonadism and pre-existing or a high risk of cardiovascular disease, showed that TRT was noninferior to placebo with respect to the incidence of major adverse cardiac events.

Lincoff AM, Bhasin S, Flevaris P, Mitchell LM, Basaria S, Boden WE, Cunningham GR, Granger CB, Khera M, Thompson IM Jr, Wang Q, Wolski K, Davey D, Kalahasti V, Khan N, Miller MG, Snabes MC, Chan A, Dubcenco E, Li X, Yi T, Huang B, Pencina KM, Travison TG, Nissen SE; TRAVERSE Study Investigators. Cardiovascular Safety of Testosterone-Replacement Therapy. ***N Engl J Med.*** 2023 Jun 16. Epub ahead of print.
https://doi.org/10.1056/nejmoa2215025

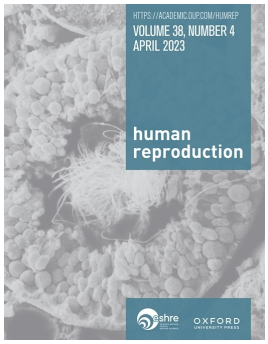
Transgender boys often receive gonadotropin-releasing hormone analogues (GnRHa) for puberty suppression before starting gender-affirming androgens. The prolonged GnRHa use in prepubertal female mice increases the body fat and impairs bone strength, but subsequent T administration reshapes the body composition and trabecular parameters to male values while restoring cortical bone's strength up to female but not male control levels.

Dubois V, Ciancia S, Doms S, El Kharraz S, Sommers V, Kim NR, David K, Van Dijck J, Valle-Tenney R, Maes C, Antonio L, Decallonne B, Carmeliet G, Claessens F, Cools M, Vanderschueren D. Testosterone Restores Body Composition, Bone Mass, and Bone Strength Following Early Puberty Suppression in a Mouse Model Mimicking the Clinical Strategy in Trans Boys. ***J Bone Miner Res (JBMR)*** 2023 May 24. Epub ahead of print.
https://doi.org/10.1002/jbmr.4832

Testosterone (T) treatment in adolescents is not easy to optimise because of the paucity of pharmacokinetic data. Allometric scaling from adult men can be a solution, as shown in this study, which used this modelling method to optimise T administration in adolescents.

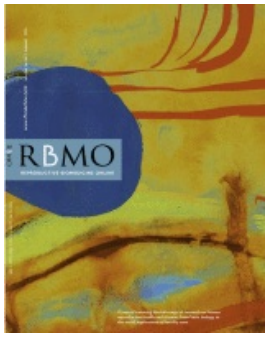
Vogiatzi MG, Jaffe JS, Amy T, Rogol AD. Allometric Scaling of Testosterone Enanthate Pharmacokinetics to Adolescent Hypogonadal Males (IM and SC Administration). ***J Endocr Soc*** **(JES)** 2023 Apr 27;7(6):bvad059.

https://doi.org/10.1210/jendso/bvad059



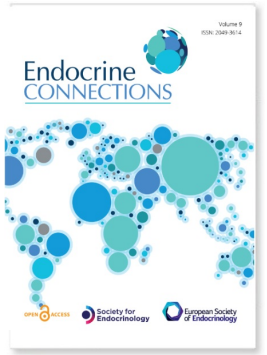
A multi-centre cross-sectional study was carried out in 117 men with idiopathic NOA undergoing mTESE. A higher likelihood of successful sperm retrieval was observed in men with lower preoperative serum anti-Müllerian hormone (AMH) levels, with good predictive accuracy achieved using an AMH threshold of <4 ng/ml.

Pozzi E, Raffo M, Negri F, Boeri L, Saccà A, Belladelli F, Cilio S, Ventimiglia E, d'Arma A, Pagliardini L, Viganò P, Pontillo M, Lucianò R, Colecchia M, Montorsi F, Alfano M, Salonia A. Anti-Müllerian hormone predicts positive sperm retrieval in men with idiopathic non-obstructive azoospermia - findings from a multi-centric cross-sectional study. ***Hum Reprod.*** 2023 Jun 15:dead125. Epub ahead of print.
https://doi.org/10.1093/humrep/dead125



This prospective study found that only small fractions of patients with obstructive azoospermia or NOA needed testosterone replacement therapy (TRT) after TESE, but 36% of men with Klinefelter syndrome required TRT. Irrespective of the diagnosis, a higher T concentration before TESE was associated with a lower chance of needing TRT.

Eliveld J, van der Bles I, van Wely M, Meißner A, Soufan AT, Heijboer AC, Repping S, van der Veen F, van Pelt AMM. The risk of hypogonadism after testicular sperm extraction in men with various types of azoospermia: a prospective cohort study. ***Reprod Biomed Online***. 2023 Jun;46(6):973-981.
https://doi.org/10.1016/j.rbmo.2023.02.003



Congenital adrenal hyperplasia (CAH) is a recessive condition that affects the adrenal glands and can impair testis function. This study found a significant reduction in serum concentrations of INSL3, testosterone, inhibin B and AMH in adult males with CAH. Serum INSL3 was particularly reduced in men with testicular adrenal rest tumors.

Johannsen TH, Albrethsen J, Neocleous V, Baronio F, Cools M, Aksglaede L, Jørgensen N, Christiansen P, Toumba M, Fanis P, Ljubicic ML, Juul A. Reduced serum concentrations of biomarkers reflecting Leydig and Sertoli cell function in male patients with congenital adrenal hyperplasia. ***Endocr Connect.*** 2023 May 1:EC-23-0073. Epub ahead of print.
https://doi.org/10.1530/ec-23-0073

High levels of oxidative stress and DNA fragmentation (DF) were found in sperm of patients with cancer. The authors recommend that the detection of oxidative stress is a part of the management of reproductive issues in cancer patients.

Calamai C, Ammar O, Rosta V, Farnetani G, Zimmitti S, Giovannelli L, Vignozzi L, Krausz C, Muratori M. Testicular and Haematological Cancer Induce Very High Levels of Sperm Oxidative Stress. ***Antioxidants***. 2023; 12(6):1145.
https://doi.org/10.3390/antiox12061145

Cadmium (Cd) can accumulate in spermatozoa and reduce total motile sperm fraction in exposed men compared to not-exposed controls. It is important to reduce the exposure.

Pappalardo C, Cosci I, Moro G, Stortini AM, Sandon A, De Angelis C, Galdiero G, Trifuoggi M, Pivonello R, Pedrucci F, Di Nisio A, Foresta C, Ferlin A, De Toni L. Seminal cadmium affects human sperm motility through stable binding to the cell membrane. ***Front Cell Dev Biol.*** 2023 May 18;11:1134304.

https://doi: 10.3389/fcell.2023.1134304

Journal of Clinical Medicine

A call is made for routine uro-andrological assessment of young men to ameliorate male health. This is based on a study of 157 supposedly healthy young men who have never been seen by a urologist.

In this cohort, 45% men had abnormal semen analysis, 20% had signs of varicocele, 4 patients were diagnosed with hypogonadism and 2 with testicular cancer.

Puliatti S, Toso S, Ticonosco M, Rabito S, Sighinolfi MC, Ferrari R, Rochira V, Santi D, Trenti T, Navarra M, Ferretti S, Montano L, Micali S. Semen Analysis in "Urology-Naïve" Patients: A Chance of Uroandrological Screening in Young Males. ***J Clin Med.*** 2023 Jun 1;12(11):3803. https://doi.org/10.3390/jcm12113803

Androgenetics and translational/basic andrology

Two exciting studies concerning the Y chromosome. Loss of the Y chromosome observed in multiple cancer types (and occurring naturally in older men) correlated with aggressivity of bladder cancer. Y-negative cancer cells could promote T cell exhaustion and evade detection by the immune system. In the second study, a Y-chromosome gene (histone demethylase *KDM5D*) was linked in mice to increased spread of colorectal cancers with *KRAS* mutations, because of disruption of cell adhesion and evading $CD8^+$ T cells. Together, the studies suggest that genetic factors — not just lifestyle — are responsible for the male bias that many cancers have.

Commentary: Ledford H. How the Y chromosome makes some cancers more deadly for men. ***Nature***. 2023 Jun 21. https://doi.org/10.1038/d41586-023-01987-x
1. Abdel-Hafiz HA, Schafer JM, Chen X, Xiao T, Gauntner TD, Li Z, Theodorescu D. Y chromosome loss in cancer drives growth by evasion of adaptive immunity. ***Nature*** 2023 Jun 21. Epub ahead of print.
https://doi.org/10.1038/s41586-023-06234-x
2. Li J, Lan Z, *et al.* et Wang A, DePinho RA. Histone demethylase KDM5D upregulation drives sex differences in colon cancer. ***Nature*** 2023 Jun 21. Epub ahead of print.
https://doi.org/10.1038/s41586-023-06254-7

nature COMMUNICATIONS

Recessive variants in *SART3* were identified in 9 individuals with intellectual disability and 46,XY gonadal dysgenesis. *SART3* encodes a well-conserved RNA binding protein that is critical to spliceosome function. The authors proposed to term the condition INDYGON syndrome (**I**ntellectual disability, **N**eurodevelopmental defects and **D**evelopmental delay with 46,X**Y** **GON**adal dysgenesis).

Ayers, K.L., Eggers, S., Rollo, B.N. *et al.* et BenZeev, B., Sinclair, A.H. Variants in SART3 cause a spliceosomopathy characterised by failure of testis development and neuronal defects. ***Nature Commun*** 14, 3403 (2023).
https://doi.org/10.1038/s41467-023-39040-0

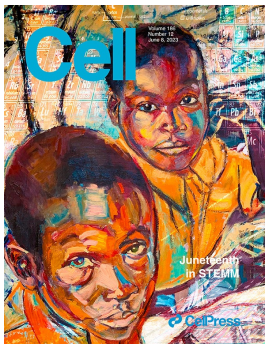
This study performed exome sequencing and gene burden analysis in a large cohort of patients with familial or bilateral testicular cancer. Novel genes variants were identified, including protein-coding, consistent with multigenic heritability. The results suggest potentially druggable targets for TGCT prevention or treatment.

Pyle LC, Kim I, et al et, Regeneron Genetics Center Research Team, Cancer Genomics Research Laboratory, Greene MH, Nathanson KL, Stewart DR. Germline Exome Sequencing for Men with Testicular Germ Cell Tumor Reveals Coding Defects in Chromosomal Segregation and Protein-targeting Genes. ***Eur Urol.*** 2023 May 26:S0302-2838(23)02813-0. Epub ahead of print.
https://doi.org/10.1016/j.eururo.2023.05.008

Commentary: Almstrup K, Rajpert-De Meyts E. Sequencing Identifies Novel Genetic Variants Associated with High-risk Testicular Cancer. Eur Urol. 2023 Jun 2:S0302-2838(23)02881-6.
https://doi.org/10.1016/j.eururo.2023.05.035

A six-gene copy number classifier proposed in the study of 448 patients and previously published datasets from radical prostatectomies. The classifier performs better than conventional stratification methods, is low cost, and can be performed easily in clinical laboratories.

Ebrahimizadeh W, Guérard KP, Rouzbeh S, Scarlata E, Brimo F, Patel PG, Jamaspishvili T, Hamel L, Aprikian AG, Lee AY, Berman DM, Bartlett JMS, Chevalier S, Lapointe J. A DNA copy number alteration classifier as a prognostic tool for prostate cancer patients. ***Br J Cancer*** 128, 2165–2174 (2023). https://doi.org/10.1038/s41416-023-02236-8
Editorial summary: Lautert-Dutra, et al. Precision medicine for prostate cancer—improved outcome prediction for low-intermediate risk disease using a six-gene copy number alteration classifier. ***Br J Cancer*** 128, 2163–2164 (2023). https://doi.org/10.1038/s41416-023-02289-9



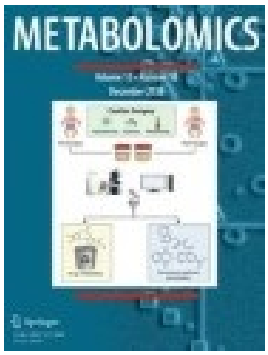
Sperm motility depends on the axoneme. This excellent study presented high-resolution structures of axonemal doublet microtubules (DMT) from two different species and analysed conserved DMT proteins, some linked to mammalian infertility.

Leung MR, Zeng J, Wang X, Roelofs MC, Huang W, Zenezini Chiozzi R, Hevler JF, Heck AJR, Dutcher SK, Brown A, Zhang R, Zeev-Ben-Mordehai T. Structural specializations of the sperm tail. ***Cell***. 2023 Jun 13:S0092-8674(23)00576-7. Epub ahead of print.
https://doi.org/10.1016/j.cell.2023.05.026

Retinoic acid (RA) is the proposed factor inducing mammalian meiosis. Using a mouse model, this study found that although RA is required for spermatogonial differentiation and spermiogenesis, it is dispensable for the initiation or completion of male meiosis.

Kirsanov O, Johnson TA, Niedenberger BA, Malachowski TN, Hale BJ, Chen O, Lackford B, Wang J, Singh A, Schindler K, Hermann BP, Hu G, Geyer CB. Retinoic acid is dispensable for meiotic initiation but required for spermiogenesis in the mammalian testis. ***Development***. 2023 Jun 23:dev.201638. Epub ahead of print.
https://doi.org/10.1242/dev.201638

Methodology



The use of metabolomics to study the composition of the seminal fluid is a promising approach to gain insight into semen quality. This study identified several compounds (including acyl-carnitines, steroids, and other lipids) that can distinguish samples provided by individuals exhibiting low or high sperm counts.

Olesti E, Boccard J, Rahban R, Girel S, Moskaleva NE, Zufferey F, Rossier MF, Nef S, Rudaz S, González-Ruiz V. Low-polarity untargeted metabolomic profiling as a tool to gain insight into seminal fluid. ***Metabolomics***. 2023 Jun 5;19(6):53.
https://doi.org/10.1007/s11306-023-02020-y

Book of the month

The latest special issue of ***Andrology*** (July 2023) edited by Kate Loveland and Wei Yan, contains 16 articles provided by speakers at the XXVIth North American Testis Workshop (May 4-7, 2022, La Jolla, California). The articles cover regulation of mammalian spermatogenesis, including small RNAs and epigenetic factors, possible targets for non-hormonal contraception, (dys)function of Leydig cells and Sertoli cells, and sperm interaction with the female reproductive tract.

New Horizons in Testis Biology and Men's Health

Introduction by Yan & Loveland:
https://doi.org/10.1111/andr.13462

European Academy of Andrology
Office: Szent István Krt. 7., 1055, Budapest, Hungary