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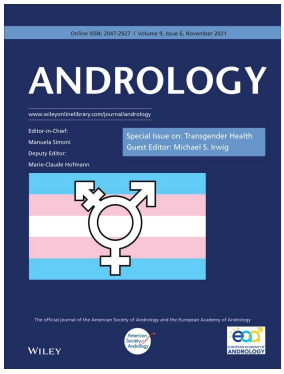
EAA Literature Alert
Edition November 2021

Andrologists have been very productive lately! Hence, this edition is larger than usual. We highly recommend reading two special issues of *Andrology* filled to the brim with excellent articles addressing: 1) andrological imaging and 2) transgender health. In addition, several EAA training centres produced interesting studies and review articles.

Special issues of *Andrology*

Special Issue of *Andrology* on andrological imaging contains 16 high-quality articles from leading groups, which give state-of-the-art in the field. Among the techniques covered in this issue are B-mode-, Doppler-, contrast-enhanced scrotal ultrasound, dynamic penile duplex ultrasound, multiparametric imaging, magnetic resonance imaging (MRI), FDG-PET/CT, and elastography. The issue should be read by all specialists using imaging to diagnose and monitor andrological disorders.

Special Issue: Imaging in Andrology, *Andrology*, 2021; 9(5), 1278-1289.
https://onlinelibrary.wiley.com/toc/20472927/2021/9/5
Editorial comment: Isidori AM, Dogra VS, Sidhu PS. Imaging andrology of the future: Where functional imaging embraces the clinic. ***Andrology***, https://onlinelibrary.wiley.com/doi/full/10.1111/andr.13054

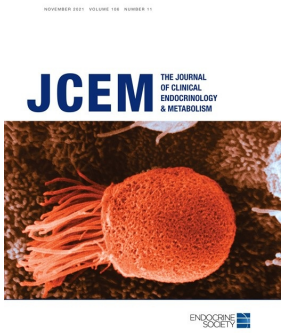


This just-published special issue of *Andrology* reviews current knowledge of the medical, surgical, reproductive, and psychological issues pertaining to transgender and gender diverse (TGD) patients. The issue contains 14 papers, including original studies and review articles, from leading groups around the world. The papers cover various aspects of TGD starting from early adolescence, so in addition to andrologists, this issue will be of interest to pediatricians and pediatric urologists.

Special issue: Transgender Health, *Andrology*, 2021; 9(6), 1673-1957.
https://onlinelibrary.wiley.com/toc/20472927/2021/9/6
Editorial comment: Irwig MS. The growing and interdisciplinary field of transgender health. ***Andrology***, https://onlinelibrary.wiley.com/doi/full/10.1111/andr.13114

Clinical andrology and epidemiology

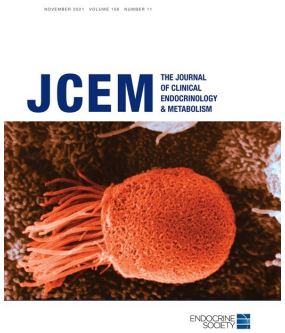
A new article from the European Ageing Men Study (EMAS). The study investigated an association of total and free 25(OH)D and 1,25(OH) 2 D concentrations with survival status in 1,915 men, aged 40-79 years. Men with vitamin D deficiency (a large proportion of subjects in the study's cohort) had a twofold



increased mortality risk, regardless of the fraction of vitamin D measured.

Dejaeger M, Antonio L, Bouillon R, Moors H, Wu FCW, O'Neill TW, Huhtaniemi IT, Rastrelli G, Forti G, Maggi M, Casanueva FF, Slowikowska-Hilczer J, Punab M, Gielen E, Tournoy J, Vanderschueren D. Ageing men with insufficient vitamin D have a higher mortality risk: no added value of its free fractions or active form. ***J Clin Endocrinol Metab***. 2021 Oct 18:dgab743. doi: 10.1210/clinem/dgab743. Epub ahead of print. PMID: 34662423.

academic.oup.com/jcem/advance-article-abstract/doi/10.1210/clinem/dgab743/6400270?redirectedFrom=fulltext



Dehydroepiandrosterone sulfate (DHEAS) substantially decreases with age, which may accelerate osteoporosis. This study investigated association of DHEAS (in connection with several known SNPs), bone mineral density (BMD) and fractures. DHEAS was associated with increased BMD and decreased fractures. DHEAS may play a protective role in decreasing fracture risk, mainly by increasing bone mass.

Yokomoto-Umakoshi M, Umakoshi H, Iwahashi N, Matsuda Y, Kaneko H, Ogata M, Fukumoto T, Terada E, Nakano Y, Sakamoto R, Ogawa Y. Protective Role of DHEAS in Age-related Changes in Bone Mass and Fracture Risk: A Mendelian Randomization Study. ***J Clin Endocrinol Metab.*** 2021 Jun 22:dgab459. doi: 10.1210/clinem/dgab459. Epub ahead of print. PMID: 34157116.

https://doi.org/10.1210/clinem/dgab459

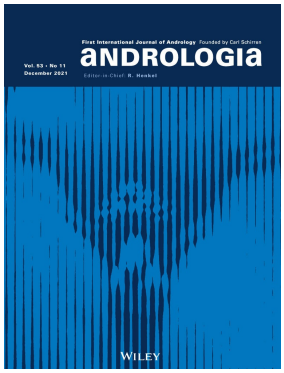
This Danish study assessed differences in treatment regimens using long-acting testosterone undecanoate (TU) and the risk of adverse outcomes in younger versus elderly testosterone-deficient patients. TU dose has to be carefully adjusted in the elderly patients to reach treatment targets and avoid polycythemia.

Abildgaard J, Petersen JH, Bang AK, Aksglaede L, Christiansen P, Juul A, Jørgensen N. Long-term testosterone undecanoate treatment in the elderly testosterone deficient male - an observational cohort study. ***Andrology.*** 2021 Nov 7. doi: 10.1111/andr.13124. Epub ahead of print. PMID: 34743411.

This large retrospective Italian study evaluated whether conventional semen parameters could predict the ART success. The authors found that sperm motility played a role in predicting in vitro fertilization (IVF) success, while sperm morphology could predict successful outcomes of intracytoplasmic sperm injection (ICSI).

Villani MT, Morini D, Spaggiari G, Falbo AI, Melli B, La Sala GB, Romeo M, Simoni M, Aguzzoli L, Santi D. Are sperm parameters able to predict the success of assisted reproductive technology? A retrospective analysis of over 22,000 assisted reproductive technology cycles. ***Andrology*** 2021 Nov 1. doi: 10.1111/andr.13123. Epub ahead of print. PMID: 34723422.
https://doi.org/10.1111/andr.13123

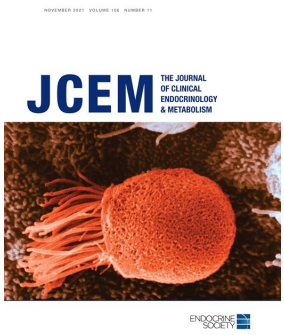
This study from the EAA Centre in Lodz found that a diet supplement containing glutathione and herbs with antioxidative and antioestrogenic activity, in combination with lifestyle changes, led to improvement of reproductive hormone values and mean semen parameters in men with mild idiopathic semen abnormalities. This treatment may be suitable for the first-line therapy for such patients.



Slowikowska-Hilczer J, Walczak-Jedrzejowska R, Dobronski P. The influence of a combination of lifestyle modification and a new formula supplement with antioxidative and antioestrogenic activity on mild idiopathic abnormalities of semen parameters-A pilot study. ***Andrologia*** 2021 Oct 18:e14279. doi: 10.1111/and.14279. Epub ahead of print. PMID: 34664304.
https://doi.org/10.1111/and.14279

This study from the EAA Centre in Estonia evaluated 5014 boys born and followed up at Tartu University Hospital. The data revealed that the prevalence of cryptorchidism, especially in full-term boys, is lower in Estonia than reported in the other Nordic-Baltic countries and worldwide.

Kübarsepp V, Varik K, Varendi H, Antson A, Veinla M, Nellis G, Merila M, Salundi U, Astover V, Punab M. Prevalence of congenital cryptorchidism in Estonia. ***Andrology*** 2021 Oct 26. doi: 10.1111/andr.13121. Epub ahead of print. PMID: 34699126.
https://doi.org/10.1111/andr.13121



Childhood obesity can negatively affect testosterone levels and penis development. This Italian study of 1130 boys and adolescents found that at puberty, penile length was significantly decreased, with concomitantly reduced testosterone levels in obese boys when compared to normal-weight boys.

Mancini M, Pecori Giraldi F, Andreassi A, Mantellassi G, Salvioni M, Berra CC, Manfrini R, Banderali G, Folli F. Obesity Is Strongly Associated With Low Testosterone and Reduced Penis Growth During Development. ***J Clin Endocrinol Metab.*** 2021 Oct 21;106(11):3151-3159. doi: 10.1210/clinem/dgab535. PMID: 34283215.
https://doi.org/10.1210/clinem/dgab535

COVID-19

This review article discusses the reasons for a higher mortality rate from COVID-19 in men vs women. A variety of biological, social and economic factors have contributed to this sex disparity. The authors make a compelling argument for a streamlined men's health programme.

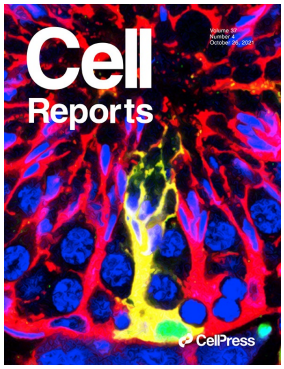
Tharakan T, Khoo CC, Giwercman A, Jayasena CN, Sofikitis N, Salonia A, Minhas S. Are sex disparities in COVID-19 a predictable outcome of failing men's health provision? ***Nature Reviews Urology*** 2021 Nov 18:1–17. doi: 10.1038/s41585-021-00535-4. Epub ahead of print. PMID: 34795426.

Translational and basic andrology

Conventional therapies for epididymitis and

orchitis using antibiotics are often ineffective or cause side effects. The group behind this study screened the secretin family G protein–coupled receptors (GPCRs) expressed in the testis and epididymis. They found that activation of type 1 parathyroid hormone receptor (PTH1R) by abaloparatide (an osteoporosis drug) effectively alleviated mumps virus- or lipopolysaccharide inflammatory responses in testis and epididymis, and improved sperm function in both mouse model and human samples.

Wang MW, Yang Z, Chen X, Zhou SH, Huang GL, Sun JN, Jiang H, Xu WM, Lin HC, Yu X, Sun JP. Activation of PTH1R alleviates epididymitis and orchitis through Gq and β-arrestin-1 pathways. ***Proc Natl Acad Sci USA (PNAS)*** 2021 Nov 9;118(45):e2107363118. doi: 10.1073/pnas.2107363118. PMID: 34740971.
https://www.pnas.org/content/118/45/e2107363118



An important study demonstrated a link between an environmental insult and rapid alterations in the sperm epigenome. The team from Australia found in mice that acute acrylamide exposure caused alterations in epididymal proteome and sperm-borne sncRNAs during epididymal sperm transition. Spermatozoa from acrylamide-exposed animals used for fertilisation compromised the transcriptomic profile of early embryos. The study highlights the importance of pre-conception male health.

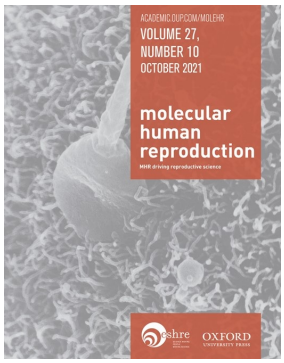
Trigg NA, Skerrett-Byrne DA, Xavier MJ, Zhou W, Anderson AL, Stanger SJ, Katen AL, De Iuliis GN, Dun MD, Roman SD, Eamens AL, Nixon B. Acrylamide modulates the mouse epididymal proteome to drive alterations in the sperm small non-coding RNA profile and dysregulate embryo development. ***Cell Reports*** 2021 Oct 5;37(1):109787. PMID: 34610313.
https://doi.org/10.1016/j.celrep.2021.109787

In a parallel study, the same Australian group and collaborators found marked changes in the transcriptome profile of seminal vesicles isolated from acutely acrylamide-exposed animals. This study provided one of the first gene expression profiles of normal mouse seminal vesicles.

Skerrett-Byrne DA, Nixon B, Bromfield EG, Breen J, Trigg NA, Stanger SJ, Bernstein IR, Anderson AL, Lord T, Aitken RJ, Roman SD, Robertson SA, Schjenken JE. Transcriptomic analysis of the seminal vesicle response to the reproductive toxicant acrylamide. ***BMC Genomics.*** 2021 Oct 8;22(1):728. PMID: 34625024.
https://bmcgenomics.biomedcentral.com/articles/10.1186/s12864-021-07951-1

This study presented evidence that *in vitro* human somatic cells can be converted to male germline stem cells by the defined factors. The authors claimed that they reprogramed human Sertoli cells into cells with the characteristics of human spermatogonial stem cells (SSCs) by lentiviral transfection forcing overexpression of DAZL, DAZ2, and BOULE. The transfected SSC-like cells could proliferate in nude mice and differentiate into spermatocytes and haploid spermatids in vitro.

Zhang W, Chen W, Cui Y, Wen L, Yuan Q, Zhou F, Qiu Q, Sun M, Li Z, He Z. Direct reprogramming of human Sertoli cells into male germline stem cells with the self-renewal and differentiation potentials via overexpressing DAZL/DAZ2/BOULE genes. ***Stem Cell Reports*** 2021 Oct 12:S2213-6711(21)00488-4. doi: 10.1016/j.stemcr.2021.09.011. Epub ahead of print. PMID: 34653405.
https://doi.org/10.1016/j.stemcr.2021.09.011



PINK3 from mouse seminal vesicles was reported to suppress in vitro sperm capacitation. This study identified testicular serine protease 1 (TESP1) as the receptor for SPINK3. If confirmed, the SPINK3-TESP1 system can be a candidate pathway for development of a male contraceptive.

Ramachandran SS, Balu R, Vilwanathan R, Jeyaraman J, Paramasivam SG. A mouse testis serine protease, TESP1, as the potential SPINK3 receptor protein on mouse sperm acrosome. ***Mol Hum Reprod***. 2021 Sep 29;27(10):gaab059. PMID: 34524424. https://doi.org/10.1093/molehr/gaab059

life

This study from the EAA Centre in Zagreb performed a careful evaluation of morphometric features and proliferation of Leydig cells in patients with non-obstructive vs obstructive azoospermia (NOA vs OA).
Leydig cells in NOA patients formed larger clusters and displayed hypertrophy but no proliferation, leading to an actual decrease in the LC number. The authors attributed this to inflammatory changes and consequent interstitial fibrosis frequently associated with NOA.

Hauptman D, Perić MH, Marić T, Katušić Bojanac A, Nino Sinčić N, Zimak Z, Kaštelan Ž, Ježek S. Leydig Cells in Patients with Non-Obstructive Azoospermia: Do They Really Proliferate? ***Life*** 2021; 11, 1266. https://doi.org/10.3390/life11111266

Not strictly andrology, but a fascinating breaktrough reporting the existence of a transcription dependent, genome surveillance system that provides immediate protection against newly acquired mobile genetic elements while avoiding inappropriate repression of host genes. This study showed that the HUSH complex epigenetically silences long intronless sequences which are typical for retrotransposons or other RNA-derived 'non-self' elements. This is a new mechanism of rapid silencing 'invading' transgenes in various cell types, including potentially germ cells (which normally use piRNAs as a long-term adaptive protection system).

Seczynska M, Bloor S, Cuesta SM, Lehner PJ. Genome surveillance by HUSH-mediated silencing of intronless mobile elements. ***Nature***. 2021 Nov 18. doi: 10.1038/s41586-021-04228-1. Epub ahead of print. PMID: 34794168.

Androgenetics

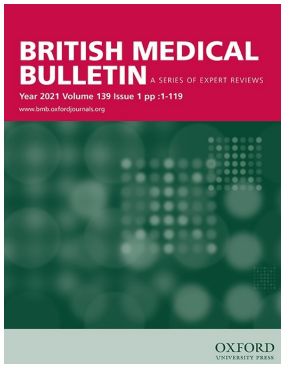
ACTL7A, an actin-related protein, is essential for spermatogenesis. This study identified novel compound heterozygous variants in ACTL7A as a causative factor for human total fertilisation failure in one family. Artificial oocyte activation after ICSI was performed and a healthy live birth was obtained.

Wang J, Zhang J, Sun X, Lin Y, Cai L, Cui Y, Liu J, Liu M, Yang X. Novel bi-allelic variants in ACTL7A are associated with male infertility and total fertilization failure. ***Human Reproduction*** 2021 Nov 18; 36(12): 3161-3169. doi: 10.1093/humrep/deab228. PMID: 34727571. https://doi.org/10.1093/humrep/deab228

frontiers in Cell and Developmental Biology

Ankyrin ANKRD31 is involved in meiotic recombination and male germ cell progression. Here, the authors showed that Ankrd31$^{-/-}$ mice were infertile and exhibited oligo-astheno-teratozoospermia, and displayed a complete deregulation of blood-epididymal barrier.

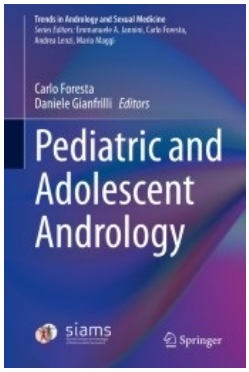
Manfrevola F, Martinez G, Coutton C, Rocco D, Reynaud K, Le Vern Y, Froment P, Beauclair L, Aubert D, Pierantoni R, Chianese R, Guillou F. Ankrd31 in Sperm and Epididymal Integrity. ***Frontiers Cell Dev Biol.*** 2021 Nov 8;9:741975. doi: 10.3389/fcell.2021.741975. PMID: 34820371.
https://www.frontiersin.org/articles/10.3389/fcell.2021.741975/full



This review article from the EAA Centre in Tartu summarized the recently published literature regarding the genetic causes of male infertility. The authors call for more systematic sequencing studies and multidisciplinary clinical guidelines to improve molecular diagnostics in the routine management of infertile men.

Laan M, Kasak L, Punab M. Translational aspects of novel findings in genetics of male infertility-status quo 2021. ***Brit Med Bull.*** 2021 Nov 9:ldab025. doi: 10.1093/bmb/ldab025. Epub ahead of print. PMID: 34755838.
https://doi.org/10.1093/bmb/ldab025

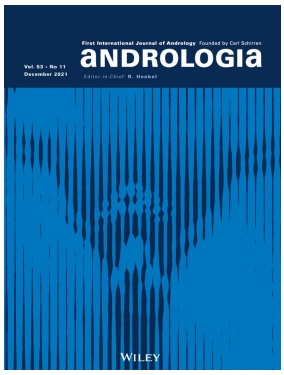
Books



"Pediatric and Adolescent Andrology", edited by EAA members C. Foresta and D. Gianfrilli, provides comprehensive coverage of the latest knowledge, current guidelines, and expert consensus on paediatric and adolescent andrology. This compendium will be of interest to andrologists, endocrinologists, paediatricians and urologists.

The book, published by Springer Nature Switzerland, is available as a printed edition or an eBook:
eBook ISBN: 978-3-030-80015-4; Print ISBN: 978-3-030-80014-7
https://link.springer.com/book/10.1007/978-3-030-80015-4?sap-outbound-id=34550F565BDC64C5D9B67EDC532B0FB0BE7C6E5F

Case reports of the month



This report describes a case of leiomyoadenomatoid tumour of the epididymis, a very rare, benign histological entity. The mass was enucleated with a conservative surgery sparing the testis. This case highlights the importance for both pathologists and urologists to be aware of these benign tumours, to avoid misdiagnosis during intraoperative consultation and radical surgical procedures, such as radical orchiepididymectomy.

Lucianò R, Tenace NP, Pederzoli F, Alfano M, Colecchia M, Montorsi F, Doglioni C, Salonia A. Leiomyoadenomatoid tumours of the epididymis: A new case report and review of the literature. ***Andrologia*** 2021 Oct 17:e14280. doi: 10.1111/and.14280. Epub ahead of print. PMID: 34658055.
https://doi.org/10.1111/and.14280

This paper describes the unusual syndrome of acquired penile girth increase that encompasses two distinct etiologies; post-priapistic and idiopathic cases. In this case, the geometric approach used to surgically correct bilateral corporal herniation proved successful.

Pescatori ES, Drei B, Rabito S. Circumferential Acquired Macropenis: Definition, Literature Review and Proposal of Geometrically-Based Reduction Corporoplasty. ***Sex Med.*** 2021 Nov 21;10(1):100460. doi: 10.1016/j.esxm.2021.100460. Epub ahead of print (expected Feb 2022). PMID: 34818603.

https://authors.elsevier.com/sd/article/S2050116121001409

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