EAA Literature Alert
Edition October 2021

In this edition, we have added a new section **Debate**, to inform you about recently published comments of the EAA members on different andrological aspects. We encourage you to voice your concerns on the pages of *Andrology* or other journals and share them with your colleagues.

Clinical andrology and epidemiology

This randomised clinical trial coordinated by the group at the Utah University concluded that 6-month folic acid (5 mg) and zinc (30 mg) supplementation is not effective at altering sperm DNA methylation, following previous reports of lack of impact of this regimen on basic semen quality parameters or live birth.

Jenkins T, Aston K, Carrell D, DeVilbiss E, Sjaarda L, Perkins N, Mills JL, Chen Z, Sparks A, Clemons T, Chaney K, Peterson CM, Emery B, Hotaling J, Johnstone E, Schisterman E, Mumford SL. The impact of zinc and folic acid supplementation on sperm DNA methylation: results from the folic acid and zinc supplementation randomized clinical trial (FAZST). ***Fertil Steril.*** 2021 Oct 13:S0015-0282(21)02047-1. Epub ahead of print. Doi: 10.1016/j.fertnstert.2021.09.009. PMID: 34656303.

https://www.fertstert.org/article/S0015-0282(21)02047-1/fulltext

A new application of an old drug. Botulinum neurotoxin (BoNT) was evaluated in the treatment of 70 patients with erectile dysfunction (ED) refractory to oral phosphodiesterase inhibitors (PDE5Is). In a randomized placebo-controlled prospective study. The treatment group showed a statistically significant improvement in their sexual function.

Abdelrahman IFS, Raheem AA, Elkhiat Y, Aburahma AA, Abdel-Raheem T, Ghanem H. Safety and efficacy of botulinum neurotoxin in the treatment of erectile dysfunction refractory to phosphodiesterase inhibitors: Results of a randomized controlled trial. ***Andrology.*** 2021 Oct 7. Doi: 10.1111/andr.13104. Epub ahead of print. PMID: 34618409.

Autologous hematopoietic stem cell transplantation (AHSCT), considered standard care in some haematopoietic malignancies, is associated with sexual dysfunction and hypogonadism. This preliminary study examined reproductive hormones and self-reported sexual function in 20 patients before and after AHSCT. The results showed a high prevalence of sexual dysfunction even before AHSCT. Androgens and estrogens were adversely affected, but with different patterns, and especially estrogen levels may help predict sexual dysfunction in this population.

Anderson LJ, Migula D, Abay R, Crabtree S, Graf SA, Matsumoto AM, Chauncey TR, Garcia JM. Androgens and estrogens predict sexual function after autologous hematopoietic stem cell transplant in men. **Andrology.** 2021 Oct 8. Doi: 10.1111/andr.13117. Epub

ahead of print. PMID: 34624176.

Men with moderate vitamin D deficiency can maintain normal testicular hormone parameters, as shown in this cohort study of 176 healthy young men from southern Poland, who were examined in the winter season.

Książek A, Mędraś M, Zagrodna A, Słowińska-Lisowska M, Lwow F. Correlative studies on vitamin D and total, free bioavailable testosterone levels in young, healthy men. ***Scientific Reports.*** 2021 Oct 12;11(1):20198. Doi: 10.1038/s41598-021-99571-8. PMID: 34642402.

This study examined the characteristics, treatments, and outcomes of 89 men with HIV and germ cell cancer (GCC) in the era of effective combination antiretroviral therapies. The long-term outcomes (5- and 10-year survival) of men with HIV-GCC were similar to those reported for men with HIV-negative GCC. Patients with HIV-GCC should be managed identically to HIV-negative patients.

Hentrich MU, Bower M, Daugaard G, Dieing A, Bickel M, Berretta M, Lesmeister F, Jurinovic V, Stoehr A, Heinzelbecker J, Krznaric I, Dieckmann KP, Necchi A, Maroto Rey P, Rockstroh JK, Brito M, Pfister D, Hoffmann C. Outcomes of men with HIV and germ cell cancer: Results from an international collaborative study. ***Cancer.*** 2021 Sep 30. Doi: 10.1002/cncr.33928. Epub ahead of print. PMID: 34592009. DOI: 10.1002/cncr.33928
https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.33928

Avoid drinking sugar-sweetened beverages. In this collaborative study (Boston and Copenhagen) of 2935 young men unaware of their reproductive health status, high intake of SSBs was associated with lower sperm concentration, lower total sperm count, and a lower ratio of serum inhibin-B/FSH.

Nassan FL, Priskorn L, Salas-Huetos A, Halldorsson TI, Jensen TK, Jørgensen N, Chavarro JE. Association between intake of soft drinks and testicular function in young men. ***Hum Reprod.*** 2021 Sep 29:deab179. doi: 10.1093/humrep/deab179. Epub ahead of print. PMID: 34585250.

https://doi.org/10.1093/humrep/deab220

Editorial comment: Messerlian C, Zhang Y. Much a do about nothing or male sperm in peril? Are sugar-sweetened beverages to blame? ***Hum Reprod.*** 2021 Sep 29:deab220. doi: 10.1093/humrep/deab220. Epub ahead of print. PMID: 34585251.

Debate

This comment discusses the advantages and shortcomings of the protocol of sperm motility evaluation in the latest edition of the WHO manual of human semen examination.

Paoli D, Pallotti F, Lenzi A, Lombardo F. Sperm motility evaluation according to WHO VI edition: moving forward turning back? ***J Endocrinol Invest.*** 2021 (Sept 21)

https://link.springer.com/article/10.1007%2Fs40618-021-01684-4

Androgenetics and translational andrology

A possible breakthrough in the understanding of the molecular basis of the pathogenesis of Klinefelter syndrome (KS)! The authors of this

study analyzed single-cell RNA-sequencing data from testicular biopsies of 12 patients with infertility, including KS. Unexpectedly, in a post-pubertal subpopulation of KS Sertoli cells, no transcription of the XIST locus was found, resulting in an increased expression of X-linked genes. The authors proposed that the loss of X inactivation in Sertoli cells at puberty may induce a cascade of rapid pathogenic changes in the KS testis.

Mahyari E, Guo J, Lima AC, Lewinsohn DP, Stendahl AM, Vigh-Conrad KA, Nie X, Nagirnaja L, Rockweiler NB, Carrell DT, Hotaling JM, Aston KI, Conrad DF. Comparative single-cell analysis of biopsies clarifies pathogenic mechanisms in Klinefelter syndrome. ***American Journal of Human Genetics.*** 2021 Oct 7;108(10):1924-1945. doi: 10.1016/j.ajhg.2021.09.001. PMID: 34626582.

cells

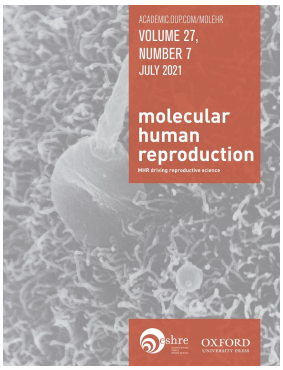
In this work, the authors studied the epigenetic markers related to chromatin silencing and meiotic sex chromosome inactivation in mice knockout models for recombination factors SPO11, DMC1, HOP2, MLH1, and the synaptonemal complex components SYCP1 and SYCP3. The results revealed numerous alterations of the dynamics of epigenetic marks and disruption of the progression of spermatocytes through meiosis.

de la Fuente R, Pratto F, Hernández-Hernández A, Manterola M, López-Jiménez P, Gómez R, Viera A, Parra MT, Kouznetsova A, Camerini-Otero RD, Page J. Epigenetic Dysregulation of Mammalian Male Meiosis Caused by Interference of Recombination and Synapsis. ***Cells.*** 2021 Sep 3;10(9):2311. doi: 10.3390/cells10092311. PMID: 34571960.
https://www.mdpi.com/2073-4409/10/9/2311

frontiers in Endocrinology

The Dutch team behind this study optimized theirs in vitro culture system of meiosis from male germline stem cells (mGSCs). They achieved a complete synapsis of meiotic chromosomes and the appearance of XY body, but meiotic recombination was still insufficient with few meiotic crossovers formed.

Lei Q, Zhang E, van Pelt AMM, Hamer G. Meiotic Chromosome Synapsis and XY-Body Formation In Vitro. ***Frontiers in Endocrinology.*** 14 October 2021, doi: 10.3389/fendo.2021.761249.
https://www.frontiersin.org/articles/10.3389/fendo.2021.761249/full



Soluble adenylyl cyclase (sAC: *ADCY*10) is required for initiating capacitation and activating motility. This study examined TDI-10229, a sAC inhibitor, and revealed that it interrupted capacitation-induced changes in ejaculated human sperm. These data identified sAC inhibitors as candidates for non-hormonal contraceptives.

Balbach M, Ghanem L, Rossetti T, Kaur N, Ritagliati C, Ferreira J, Krapf D, Puga Molina LC, Santi CM, Hansen JN, Wachten D, Fushimi M, Meinke PT, Buck J, Levin LR. Soluble adenylyl cyclase inhibition prevents human sperm functions essential for fertilization. ***Molecular Human Reproduction.*** 2021 Sep 1;27(9):gaab054. doi: 10.1093/molehr/gaab054. PMID: 34463764.

https://doi.org/10.1093/molehr/gaab054

frontiers in Endocrinology

This study investigated the effect of stress on the regulation of key genes involved in specific stages of spermatogenesis in a rat stress model and found pathological changes in the testis, including disruption of spermatogenic cells.

Tian P, Zhao Z, Fan Y, *et al. et* Hao G. Changes in Expressions of Spermatogenic Marker Genes and Spermatogenic Cell Population Caused by Stress. ***Frontiers in Endocrinology.*** October 2021, 12:584125.
10.3389/fendo.2021.584125

Male health issues outside reproduction

This excellent article reviews molecular pathways responsible for sexual dimorphism in the pathobiology of the liver, which is rarely considered in clinical studies, despite that the liver maintains metabolic homeostasis and performs endo- and xenobiotic reactions. The authors focus on non-alcoholic fatty liver disease (NAFLD), which is more severe in male than female individuals, largely due to differences in the secretion of growth hormone and steroid hormone profiles.

Lefebvre P, Staels B. Hepatic sexual dimorphism - implications for non-alcoholic fatty liver disease. ***Nature Reviews Endocrinology.*** 2021 Nov;17(11):662-670. doi: 10.1038/s41574-021-00538-6. PMID: 34417588.

https://www.nature.com/articles/s41574-021-00538-6#Abs1

Case report of the month

Current evidence suggests that testosterone-replacement therapy (TRT) in older men does not increase the risk of prostate cancer. However, in this case, because of previous TRT, the castration treatment had an insufficient effect on the patient's testosterone levels, leading to exacerbation of cancer.

Guldbaek MV, Fode M, Jensen CFS, Sønksen J, Østergren PB. 'Case of the Month' from Herlev and Gentofte Hospital, Denmark: metastatic prostate cancer in a man with late-onset hypogonadism following testosterone-replacement therapy. ***BJU Int.*** 2021 Oct;128(4):428-430. doi: 10.1111/bju.15388. PMID: 34581479.

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