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CONTACT
ESSM Secretariat
Via Ripamonti 129 – 20141 Milan, Italy
Phone: +39–02–56 601 625
Fax: +39–02–70 048 577
Email: admin@essm.org

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Welcome Address

At the end of this brilliant 2018, the ESSM looks forward to the New Year and prepares a new set of great activities.

The 2019 Ljubljana meeting is already behind the corner and promises to be a very exciting experience: Our host, Dejan Bratus, together with the scientific committee and the executive board are working very hard to fulfill and possibly exceed the high expectancies of all participants, and I'm sure they will make it!

Our scientific committee has also other important news or all ESSM members: Our society will stand more and more at the side of each member in taking difficult clinical decisions when guidelines are absent or inconclusive, providing new evidence-based European statements about specific clinical issues.

In 2019, the ESSM will be more and more a partner in your training, in your scientific research, in your literature update, in your clinical practice, and will provide you new outstanding meetings. The new year starts under very favorable auspices for all ESSM members: We can't wait to live the future of Sexual Medicine in Europe!

Ferdinando Fusco MD, PhD
Editor-in-Chief

What's new? News from the Scientific Committee of the European Society for Sexual Medicine

by Giovanni Corona and Yacov Reisman

Giovanni Corona
Endocrinology Unit,
Medical Department
Maggiore-Bellaria Hospital
Largo Nigrisoli 2
40133, Bologna, Italy

jocorona@libero.it

Yacov Reisman
Urologist, Sexologist
Chair Men's Health Clinics
Amstelland Hospital
Amstelveen, The Netherlands

uro.amsterdam@gmail.com

Sexual Medicine has tremendously expanded in the last 20 years becoming one of the most important multidisciplinary medical fields including urology, gynecology, venereology, psychiatry, cardiology, endocrinology, and primary care physician competences. One of the major aims of the European Society for Sexual Medicine (ESSM) is to guarantee and promote high standards of medical care. For this purpose in 2011 due to an initiative of the ESSM, the Union Européenne des Médecins Spécialistes (UEMS) established a Multidisciplinary Joint Committee on Sexual Medicine (MJCSM), with the primary purpose of developing the highest possible standards of training in Sexual Medicine in Europe.

In order to address this task, the ESSM Education Committee has been created to build an educational program for different levels of professions in Sexual Medicine, to increase the knowledge and quality of patient care, and to support trainees in Sexual Medicine. Finally, in 2017 ESSM launched the Young Sexual Medicine Academy (YoSeMa), a new committee to promote sexual medicine among young clinicians from various disciplines.

In line with these activities, in 2018 the Scientific Committee was renewed and expanded giving a larger space to emerging topics such as "Transgender" and introducing new topic sections such as the "New developments section" mainly related to the latest news in the field of Sexual Medicine and "New technologies and sexual function" dealing with the role and the contribution of social media and the web to our files *(https://www.essm.org/society/committees/).*

In addition, new tasks have been attributed to the Scientific Committee. In particular, after an adequate discussion, each sub-section has identified specific hot topics in the field of Sexual Medicine not covered, or only partially covered, by the current guidelines. After the initial decision, each subsection of the Scientific Committee was involved in the preparation of specific ESSM statements with the intent of providing an evidence-based European position on these specific issues. The established program includes a rigorous review process including 4 reviewers and at least 2 waves of revision. The final results will be submitted to the attention of all the presidents of the ESSM affiliated societies who can make requests for only minor changes. Finally, the final version of the statements will be presented in two different sessions at the next ESSM congress in Ljubljana for further discussion. The last version of the paper will be submitted to the official Journal of the society "The Journal of Sexual Medicine".

The first topic covered deals with "The use of the cavernous nerve injury model to study post radical prostatectomy erectile dysfunction". Several preclinical studies, using bilateral nerve sparing radical prostatectomy (NSRP) rat models, have documented that different medications (i.e. alprostadil injections, vacuum erection devices, and phosphodiesterase type 5 inhibitors etc.) are able to promote erectile function recovery, improve cavernosal smooth-muscle/collagen ratio, increase penile smooth-muscle replication, reduce penile apoptosis, preserve penile endothelial function, increase antioxidant enzymes and promote neuroprotection during and following neuropraxia. However, clinical human studies have been inconclusive. A lack of consensus among guidelines and possible pitfalls in the methodology used have led to the publication of studies whose results are often equivocal and difficult to compare. The ESSM basic science subcommittee reviewed the current state of the articles, highlighting possible pitfalls and suggesting a consensus experimental guideline for the use of the NSRP rat model.

The "Male sexual health and dysfunction" sub-committee addressed the topic related to the role of "Shockwave therapy in Sexual Medicine". In the last decade, low-intensity shockwave therapy (LISWT) has been tested in several uro-andrological diseases including erectile dysfunction (ED), Peyronie's Disease (PD) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The supposed mechanism of action is related to mechanical shear stress provoked by LISWT on the treated tissue which induces neovascularization and enhances local blood flow. Although several randomized clinical trials (RCTs) and meta-analyses have investigated the role of LISWT for the treatment of ED, PD and CPPS, the clinical significance of this treatment modality and the effect duration remain controversial within the scientific community. The ESSM reviewed the available evidence providing recommendations for the use of this approach in the field of Sexual Medicine.

The "Male and Female genito-urinary reconstructive surgery" specifically evaluated the "Penile prosthesis outcomes" providing the available evidence related to possible risk factors underlining surgery complications and the female and male short and long term expectations and overall sexual satisfaction.

The topic covered by the "Female sexual health and dysfunction" sub-committee was related to "Hormonal Contraception and female sexuality". Hormonal contraception is the most commonly reversible method used in European countries. However, its impact on female sexual function is complex and under-

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studied. The ESSM emphasized the main flaws in the current knowledge of the field providing clinicians with a practical decision-making guide for patients experiencing sexual side effects or consulting for contraception.

Another hot topic related to the female sexual function field deals with the use of "Energy-based Devices (including laser and radiofrequency) vaginal applications for genito-urinary indications" This issue has been addressed by the "New developments section". Limited pre-clinical evidence has documented that laser and radiofrequency vaginal applications can induce different histological effects on the vaginal mucosal layers. However, the depth of penetrations, the duration of cellular response and the exact underlying mechanisms of actions have still not been completely clarified. Evidence-based effects of the use of these devices on different genitourinary conditions including vulvovaginal symptoms of genitourinary syndrome of menopause, vaginal laxity and stress urinary incontinence have been reviewed providing recommendations for the use of these instruments in the field of sexual medicine.

"Sexual desire discrepancy" indicates a condition when two partners in an intimate relationship desire different levels or a different frequency of sexual activity. Although this concept was introduced decades ago and is likely as prevalent in today's sexual relationships, research on this topic is scanty. The "Sexology" section specifically addressed this important and neglected issue identifying theoretical and methodological gaps, setting priorities for future research, and making suggestions for therapeutic intervention.

The "New technologies and sexual function" sub-committee specifically evaluated the contribution of "e-health" intended as the use of information and communications technology for health in the field of Sexual Medicine addressing the role of social media in human mating behavior, the influence of electronic entertainment and sexually explicit media on sexual function, and the possible benefit of using the internet as a tool for better data acquisition in a "big data" approach.

Finally, the "Transgender section" covered another interesting topic related to "Assessment and hormonal management in adolescent and adult trans people: A focus on sexual function and satisfaction". Although, the Endocrine Society and the World Professional Association for Transgender Health have provided guidelines for gender-affirming endocrine treatment, the specific impact of hormonal treatment on sexual function and satisfaction is still poorly investigated. The ESSM performed a systematic review of the available literature specifically evaluating the impact of available treatments on sexual function and satisfaction.

The annual ESSM meeting is approaching, our President, Yacov Reisman, and me, hope to see all of you in Ljubljana enjoying the congress and the city, and participating in the ESSM Statements discussion.

Why should you come to Ljubljana for ESSM congress 2019?

by Dejan Bratus

Dejan Bratus
Dejan Bratus, MD
Urology specialist,
President of SSMS
Slovenia

brdejan@gmail.com

First of all, the scientific committee is preparing an exciting meeting with world's leading experts in all fields of Sexual Medicine. Numerous lectures, debates, round tables, workshops and courses will definitely offer interesting topics for all the participants and everyone will find some sessions tailored to one's wishes and needs. The vast number of submitted abstracts promises to make the podium and poster sessions extremely attractive as well.

Secondly, meet your colleagues during the congress and especially during the welcome reception. We promise to organize an unforgettable opening ceremony with a world class act that will not leave you untouched. It will be definitely an event that will make you remember Slovenia. The congress is organized under the honorary patronage of the President of Republic of Slovenia, Borut Pahor, which gives it a special value and makes it hard to forget.

Be a part of promoting the sexual health in one of the former East European countries. For the first time ESSM congress is taking place in this geographic region and we plan a number of events to raise the public awareness of Sexual Medicine in the area including an open air concert in the center of Ljubljana. Don't miss the opportunity to get a taste of Slovenian entertainment – you will love the energy and variety of performers.

The upcoming ESSM congress coincides with Valentine's Day. Grab the opportunity to spend it in one of the most romantic old cities in Europe. Ljubljana is considered to be both historic and modern, laid back and vibrant, peaceful and entertaining. It is one of the safest cities in the world, full of friendly locals with good foreign language skills. Its compact size makes it a logistically stress-free destination since you can walk between your hotel and most of the venues including the congress venue where the congress will take place. Ljubljana has also been named European Green Capital 2016. To be honest, February is not the best month of the year to discover the outdoor areas but the vast traffic-free area in the very center of the city which functions as a cozy city lounge with pleasant cafés, bars and restaurants is worth visiting at any time of the year.

And last, get the most value four your money. Whether you decide to do some shopping, explore Slovenian gastronomy or taste the night life of Ljubljana, you will find that you can do that for much less than in the comparable cities in Europe. Of all the ESSM congresses, this will be your cheapest beer and we are sure that getting a taste of Slovenia during the congress will make you want to come back for more in the future.

Endocrine disruption and sexual dysfunction

by Suks Minhas and Tharu Tharakan

Suks Minhas, MD FRCS (Urol)
Consultant Urologist
and Andrologist
Imperial College Healthcare
NHS Trust
London, UK

suks.minhas@nhs.net

Tharu Tharakan
Department of Urology
Imperial Healthcare NHS Trust
Charing Cross Hospital
Fulham Palace Road
London, UK

tharu.tharakan@nhs.net

Introduction

The term endocrine disrupters (EDC) was first coined in 1991 at the Wingspread Conference Centre in Racine, Wisconsin [1]. At this meeting researchers from several different disciplines came to the consensus that "a large number of man-made chemicals" have been released into the environment with the potential to "disrupt" the endocrine system of humans [1]. This followed on from several studies that had implicated environmental and household chemicals as contributing to adverse health effects in both humans and wildlife [2]. Recently, there has been a surge of research investigating the role of EDCs in human health and the Endocrine society stated in 2015 that this expansion of data "removes any doubt that EDCs are contributing to increased chronic disease burdens related to obesity, diabetes mellitus, reproduction, thyroid, cancers, and neuroendocrine and neurodevelopmental functions"[3]. Endocrine disruptors have been linked with the rise in genital malformations, adverse pregnancy outcomes and global rates of endocrine related cancers. However, this viewpoint is controversial as a joint statement by the WHO and UNEP noted that "despite substantial advances in our understanding of EDCs, uncertainties and knowledge gaps still exist that are too important to ignore" [4].

The purpose of this review is to give an overview of the relationship of endocrine disruptors and sexual function in humans.

Background and Limitations to Research

Definition

Endocrine disruptors have been defined as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations" [4]. Studies have demonstrated that EDCs can act at multiple sites in the hormone pathway including binding to the hormone receptor and acting on proteins that regulate hormone synthesis, metabolism and delivery [4].

Methodological Issues

There are several factors that complicate the investigation of EDC exposure in human health. The potential pathological mechanisms of EDCs remain complicated and experimental studies have cited non-monotonic dose response relationships [5]. This goes against the conventional toxicological risk stratification which attempts to calculate a "safe" level of a toxin [6] and hence further approaches are needed to assess EDCs. In addition to this, EDCs are ubiquitous within the environment and households with an estimated "1000" manufactured chemicals potentially having endocrine-acting properties [7]. Examples range from Phthalates used in children toys, food containers and household curtains to Dichlorodiphenyltrichloroethane (DDT) used in pesticides. The Endocrine society noted that biomonitoring shows nearly 100% of humans have a chemical body burden [8] and a study by Dodson et al demonstrated 50 potential EDCs in a range of cosmetics, personal care products, cleaners, sunscreens, and vinyl products [9]. This highlights the difficulty in assessment of single exposures. Moreover, careful consideration needs to be given to the potential interaction of EDCs with each other or chemicals within the environment or the body. These interactions could be additive, synergistic or antagonistic [10]. Given there is a growing number of chemicals being identified as EDCs and many further unknown this highlights another evaluation issue.

Several EDCs have short half lives meaning that there is large within-subject variability. As such even 24 hour urine collections have been deemed inaccurate in investigating EDC exposure [11].

Collectively, the aforementioned factors highlight the various methodological issues related to EDC assessment. Several studies have acknowledged this and there is an emerging movement towards EDC specific study protocols [10].

The number of suspected adverse health effects of EDCs is vast and outside the remits of this review. We will focus on some of the wider publicised EDCs and the associations with sexual dysfunction. We have classified the EDCs based on examples of potential exposures to humans.

Medications

Diesthylstilbestrol (DES) is a high profile pharmaceutical example of endocrine disruptors that has resulted in developmental and reproductive abnormalities in humans. DES was the first synthetic non-steroidal oestrogen and was initially advertised to prevent miscarriage. However, DES use was associated with an increased risk of clear cell vaginal carcinoma in females whose mothers had taken DES during pregnancy [12]. Moreover, DES exposed daughters have been shown to have abnormalities in their genital tract [13] [14] and an increased risk of infertility [15].

Studies have demonstrated an association with in utero DES exposure and cryptorchidism in boys[16] [17] [18]. However, the current evidence linking DES to testicular cancer and infertility in exposed sons are conflicting [13].

Pesticides

Tyrone Hayes studied the impact of low doses of Atrozene (a herbicide) on frogs and identified that it produced sexual abnormalities. He

noted that up to 20% of animals suffered from multiple gonads (up to 6 in a single animal) or were hermaphrodites [19]. This study was featured in a legal action against Syngernta (manufacture of Atrozene) and was a seminal case in public outcry at the role of potential environmental EDCs. However, Goodman et al performed a systematic review of the human studies linking Atrozene with pregnancy outcomes and noted the quality of data was poor on the basis that most studies used aggregate rather than individual-level information [20].

Topperia and Skelteberg postulated the testicular dysgenesis syndrome theory to unify increasing rates of testicular cancer, infertility and reproductive abnormalities as a results of endocrine "disruption of embryonal programming and gonadal development during foetal life" [21]. They noted that animal studies investigating the impact of exposure to vinclozolin demonstrated an association with reproductive abnormalities. Vinclozolin is a fungicide that has been shown at low levels to produce subtle alterations in sexual differentiation of the external genitalia, ventral prostate, and nipple tissue in male rat offspring [22]. Uzumcu et al demonstrated that vinclozolin exposure may have different effects depending on the time exposure. Transient exposure of vinclozolin to pregnant rats between embryonic days 8 – 14 (a period of sex determination and testis morphogenesis) resulted in germ cell apoptosis and reduction in sperm motility later in life. However, this did not impact fertility compared to control animals [23].

Interestingly, research by Anway et al highlighted that the impact of vinclozolin on human health may be transgenerational. In his study they demonstrated that vinclozolin exposure to a pregnant rat resulted in the adult sons having a decreased sperm number and increased incidence of male infertility. These effects were transmitted via the male germ line to the majority of all subsequent male generations [24]. This highlights another facet to the complexity of EDCs assessment in that the effect can present years or generations following the initial exposure.

Unfortunately, there are limited studies on the impact of intrauterine vinclozolin exposure in humans.

There is growing research exploring the relationship of cryptorchidism with exposure to EDCs. Studies have linked rates of cryptorchidism to areas with higher levels of pesticide use. However, these studies were limited by methodical issues namely selection bias and also the classification of the municipalities based on pesticide use [25] [26]. Other studies evaluating biochemical and histological levels of pesticides (Heptachloroepoxide and Hexachlorobenzene) in mothers of and children with cryptorchidism have had conflicting results [27] [28].

The Endocrine society noted that the research evaluating EDCs and hypospadias is inconsistent and fraught with methodical issues [3]. Rocheleau et al's meta analysis demonstrated an association between hypospadias and exposure to pesticides. However, there was potential pesticide exposure misclassification and it is not clear which chemical caused hypospadias [29].

Plastics and plasticisers

BPA

Bisphenol A (BPA) is one of the highest volume chemicals produced worldwide and present in many plastics used for food and drink storage [30]. The effects of BPA vary with the dose and time of exposure. The prenatal and neonatal period represent the most vulnerable window of exposure and may affect time of puberty [31] but also development of abnormal prostatic [32] and mammary tissues [33] which may predispose to neoplasia. However, Melnick et al noted that several large studies in animals replicated no abnormalities with low dose BPA. The authors attribute these discrepancies between various studies to different diets, strains of animals and dosing of BPA [34].

Li et al demonstrated an association between urinary levels of BPA and sexual function in 427 male workers. They found that increasing urine BPA level was associated with decreased sexual desire, more difficulty having an erection, lower ejaculation strength ($P < 0.001$), and lower level of overall satisfaction with sex life ($P < 0.01$) [35].

There are limited human studies evaluating the impact of BPA on ovarian development but animal studies suggest that it induces follicle atresia and inhibits growth [36].

Phthalate

Phthalate is predominantly used as a plasticiser (a substance added to plastics to modify its properties i.e. increase flexibility). It is in many items including household products (shampoos, soaps), children toys, packaging and medical devices. Such is its widespread use it is not surprising researchers found measurable levels of many phthalate metabolites in the general population and noted that phthalate exposure is widespread in the U.S. population [37].

Several studies have implicated phthalate as a trigger for male reproductive abnormalities in rats [38]. Research in animal studies have connected phthalate exposure with genital tract abnormalities including hypospadias, cryptorchidism and formation of areolae in men [39]. However, human studies evaluating the impact of in utero phthalate exposure to the aforementioned reproductive abnormalities are limited and conflicting.

There have been several human studies linking high urinary phthalate metabolite concentration and abnormal semen quality [40] [41]. However, the majority of these studies use phthalate metabolites as a proxy for phthalates exposure and the cohorts are based on populations of infertile men rather than the general population. Nassan et al performed a crossover-crossback prospective design utilising mesalamine medications coated

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with dibutyl phthalate (DBP) and noted that the use of DBP coated mesalamine reduced sperm motility and motile sperm count [42]. The benefits of a crossover-crossback prospective study is that it avoided the random variability and confounding that characterises most cross sectional research evaluating the impact of EDCs [43].

Polychlorinated biphenyls (PCBs)

Polychlorinated biphenyls (PCBS) are organic chloride compounds that were previously used in industry but use has since declined owing to concerns regarding adverse environmental and human effects. Despite the decline in PCB manufacturing its exposure is still prevalent owing to its long half life (an average of 18 years for heavy congeners) [44]. In the last decade there have been several human studies [40] [45] [46] evaluating the impact of PCB exposure to semen quality. Meeker et al noted that the majority of these studies have been consistent in demonstrating a negative association between PCB exposure and sperm motility [47]. However, he does advise caution with this finding as the majority of studies have a low participation rate, are cross sectional studies where the semen and PCB exposure were only measured once and also other environmental confounding factors may not have been excluded. Another inherent issue with studies evaluating the association of endocrine disruptors and semen is that there may have been a long lag time between the exposure and the manifestation of the abnormality. It is often felt that the critical period for some endocrine disruptors is in utero, but most studies reviewing the semen analysis have an adult population cohort.

Conclusion

There can be no doubt that there have been huge strides in research evaluating the impact of endocrine disruptors in the last decade. There has been an increased recognition and the formation of collaborative conferences and workshops such as the Gordon and Copenhagen meetings. Moreover, public awareness resulted in manufactures phasing BPA out of products [48]. There has been greater understanding regarding the challenges to the assessment of endocrine disruptors and this has attracted a multidisciplinary effort to generate new assessment paradigms [10]. Currently, there is a wealth of animal studies linking sexual dysfunction and reproductive abnormalities to Endocrine disruptors. However more research is needed in humans especially with a focus on the impact of different timed exposures.

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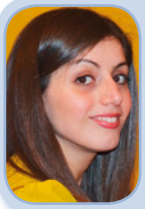
Cardiomatebolic risk and female sexual dysfunction: A gender issue

by Vincenza di Stasi, Elisa Maseroli and Linda Vignozzi



Vincenza di Stasi, MD
Sexual Medicine and Andrology Unit, Dept. Experimental and Clinical Biomedical Sciences University of Florence
Florence, Italy

Elisa Maseroli, MD
Sexual Medicine and Andrology Unit, Dept. Experimental and Clinical Biomedical Sciences University of Florence
Florence, Italy

elisameseroli@gmail.com

Linda Vignozzi, MD
Sexual Medicine and Andrology Unit, Dept. Experimental and Clinical Biomedical Sciences University of Florence
Florence, Italy

linda.vignozzi@unifi.it

The fourth International Consultation on Sexual Medicine (ICSM) established that the prevalence of women who report a Female Sexual Disorder (FSD) is approximately 40– 50%, irrespective of age. Compared with male sexuality, biologic determinants of female sexual response, in particular cardiovascular risk (CV) factors, have received scant attention. Erectile dysfunction is recognized as an opportunity for preventing CV events, and assessing the impairment of penile vascular flow by Color Doppler Ultrasound (CDU) is an important tool to ascertain CV risk. Conversely, the role of cardiovascular disease (CVD)-related genital vascular impairment remains unclear in female population. In literature, there is an increasing interest to answer to this question and in this brief report, we try to elucidate some aspects of this issue.

Endothelial dysfunction and FSD

The peripheral sexual response in women is manifested by increased blood flow leading to swelling of genital tissues, clitoral engorgement, and production of lubricating fluid transudate in the vagina; the hemodynamic mechanisms that underpin these processes are basically regulated by the tone of the vascular and non-vascular smooth muscle. Preclinical studies have constantly indicated that the nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) pathway plays a key role in modulating clitoral and vaginal blood flow. Essentially, clitoral and penile tissues share the same pattern of expression of molecular markers involved in the relaxant and contractile pathways. These data support the notion that metabolic insults could impair genital vascular function in women as observed in men. In accordance with this view, the existence of organic vasculogenic FSD syndromes has been postulated. In 1997 Park et al. defined these syndromes, typically presenting with symptoms such as vaginal discomfort with coitus, dryness and diminished sexual arousal, as “vaginal engorgement insufficiency” and “clitoral erectile insufficiency”. They hypothesized that such conditions consist of impaired hemodynamic responses to sexual efferent autonomic pelvic nerve stimulation in women with CV risk factors similar to those contributing to ED in men.

So, transposing our knowledge from one gender to the other, it was hypothesized that endothelial dysfunction contribute to vascular insufficiency even in female genital tissue. In particular, when damaged or dysfunctional, the endothelium can produce increased amounts of contracting factors and decreased amounts of relaxing factors. Metabolic syndrome and its components can contribute to these endothelial alterations. However, the relations between MetS and its single components with vasculogenic FSD and the pathologic mechanisms underpinning these relations, have yet to fully understood.

Sex steroids and FSD

The sex steroid milieu also is a pivotal regulator of the female genital response. Both estrogens and testosterone are critical for maintaining the structure and function of vaginal and clitoral tissue. Menopause-associated decrease in estrogen contributes to decreased pelvic blood flow, causing vaginal dryness and hypo-lubrication: This condition is known as Genitourinary Syndrome of Menopause. An overall age-related decrease in androgens also is observed in women, particularly in those with history of surgical menopause.

Local estrogen therapy is a universally recognized tool for contrasting vaginal dryness and atrophy. With regard to androgen therapy, a recent meta-analysis of randomized controlled trials on the effects of systemic testosterone therapy in postmenopausal women demonstrated that the use of testosterone alone or in combination with hormonal replacement therapy significantly improved multiple domains of sexual functioning, including the peripheral response.

Male vs female

The clitoris and the penis share many anatomic and histo-morphologic features. Although genital changes from increased blood flow in women are not as externally pronounced as in men, it has been demonstrated that all compartments of the vulva contain a substantial amount of erectile and non-erectile vascular tissue, with a variable, but unified, response to sexual arousal. As in penis, clitoral corpora cavernosa show smooth muscle, sinuses, and a deformable albuginea that opposes the pressure of blood flow, thus limiting the swelling and rigidity of the organ; indeed the elongation is moderate, because it does not have the same purpose as penile erection for coitus, but it is present. Then, compared with men, the vessels supplying female genitalia differ only in their smaller diameter owing to a lower hemodynamic demand.

Sex steroids probably play a pivotal role in modulating gender-related characteristics of

sexual response and cardiometabolic risk profile. Considered the reduced incidence of CV events in women compared to men up to the age of menopause, it has long been considered that endogenous estrogens exert a protective effect on the CV apparatus in contrast to androgens. However, the influence of these hormones is more complex and involves a multitude of biological processes.

The milder association between FSD and CV determinants in women compared with men might be related also to sex differences in the CV system and/or in the pathogenic mechanisms leading to CVD. Although women and men share most of the classic risk factors, the relative weighting of these in the pathogenesis of CVD can differ. Many risk factors (like smoking habit, DM and MetS) seems to take a greater CVD risk in women than in men but CVD in women is often under-recognized, leading to less aggressive treatment strategies and lower representation of women in clinical trials.

Methods to investigate peripheral vascular changes

The physiologic component of the female sexual response is typically quantified by measuring blood flow change within the genital and pelvic regions. Validated assessment techniques of vascular changes in female genitalia include indirect measures of heat dissipation, vaginal photoplethysmography and CDU. Specifically, CDU is the most recently introduced validated technique in the field and represents a quick and non-invasive tool that allows for continuous real-time assessment of anatomic and vasocongestive components of the female genitalia. Recently, clitoral PI has been further investigated in a study enrolling 71 women with FSD, which aimed to analyze the associations between basal clitoral vascularization and cardiometabolic risk factors. Notably, clitoral PI was significantly correlated with MetS (in particular Insulin Resistance), number of MetS components and obesity, independently of age, smoking habit and years of menopause; women with a higher PI, and, hence, with greater clitoral vascular resistance, reported a decreased subjective sexual arousal. According to these findings, CDU might be proposed as a reliable method of inquiry into the cardiometabolic correlates of FSD.

Conclusions

In women, cardiometabolic risk factor show a milder association with sexual dysfunction and FSD is far from being fully recognized as an independent marker of increased CV risk. To overcome gender-differences on this issue, the female genital vascular district should be extensively assessed with objective, standardized and validated methods. CDU appears a promising technique but further study are necessary to establish normative values. Longitudinal intervention trials on the effect of the treatment of CV risk factors on FSD also are urgently needed.

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Hemospermia. What you need to know man

by Oleg Apolikhin, E. A. Efremov and Yu. V. Kastrikin

Apolikhin O.I., MD, PhD
Chief specialist of the Ministry of health care of Russia in Reproductive Health, Director N. Lopatkin Scientific Research Institute of Urology, Russia

apolikhin.oleg@yahoo.com

Efremov E. A.
Dr. M.Sc., Professor of the Department of Urology, Andrology and Oncourology
Pirogov Russian National Research Medical University, Russia

konfandrology@rambler.ru

Kastrikin Yu. V.
Researcher associate of the Department of Andrology and Human Reproductive Health of Research Institute of Urology and Interventional Radiology
N.A. Lopatkin, Russia
yurii_kn@mail.ru

The problem of hemospermia is known to doctors since ancient times, and its first descriptions belong to Hippocrates and Galen.

Up to 77% of men go to the urologist after the first or second episode of the appearance of hemospermia. At the same time, in 70–80% of cases the cause of hemospermia is not detected and the spontaneous resolution of this disease is noted in 60% of cases within a month.

The concept of hemospermia refers to the presence of blood in the semen, which is caused by both anatomical and functional disorders of the male sex glands, urethra, or vas deferens.

It is necessary to distinguish between true hemospermia (haemospermia vera), in which blood evenly paints sperm in a rusty or chocolate color, as well as false hemospermia (haemospermia spuria), in which blood is mixed with sperm in the form of individual filamentous clots.

It should be noted that hemospermia occurs in men of all ages, usually from 30 to 40 years, with an average age of 37 years, and the presence of hemospermia lasts, as a rule, from one month to two years.

Nevertheless, today it is known that in most cases the appearance of hemospermia is not dangerous for men, but requires a comprehensive study, and follow-up by a doctor. The only exceptions are persons over 50 years old with suspected prostate cancer (PCa), since the appearance of hemospermia is associated with an increased risk of developing prostate cancer in men over 50 years old.

If we are talking about the causes of hemospermia, so in a separate category should be distinguished congenital causes, which include cysts of the seminal vesicles and ejaculatory tract. The group of inflammatory diseases includes urethritis, prostatitis, epididymitis, vesiculitis, condylomas of the urethra, tuberculosis, schistosomiasis and viral lesions. Also, obstruction due to post-inflammatory changes, as well as calculus, diverticula and cysts of the seminal vesicles and stricture of the urethra can also cause hemospermia. Malignant diseases should be considered: Neoplasms of the prostate gland, bladder, seminal vesicles and scrotum organs. The category of vascular factors is represented by varicose veins, hemangiomas, and sexual excesses. Traumatic causes are direct injuries, as well as the consequences of minimally invasive treatment of hemorrhoids and iatrogenic (for example, after a prostate biopsy). Also, systemic diseases may be present, such as hypertension, hemostasis pathology and taking certain medications. In many publications, von Willebrand syndrome and coagulopathy are mentioned (especially in patients with impaired liver function). Of course, you should always find out if the patient is receiving anticoagulant therapy (for example, aspirin or heparin).

What is the diagnostic algorithm for identifying the cause of hemospermia? So, the presence of hemospermia should always involve a complex urological examination. In all patients complaining about blood admixture in semen, attention should be paid to concomitant symptoms, such as pain, lower urinary tract symptoms, and it is also important to assess the likelihood of having sexually transmitted infections (epidemiological and sexual history), pay attention to blood pressure and the state of the blood coagulation system. We study in detail the history of the development of the disease, the presence of concomitant diseases, which drugs the patient has taken or is currently taking. It is important to consider the family history of the patient (especially in relation to prostate cancer), paying attention to first-degree relatives or relatives diagnosed before the age of 60, as well as coagulopathy. Next, we resort to the integrated use of laboratory and instrumental methods of research.

It is important to distinguish hemospermia from hematuria. Thus, the performance of a general urine analysis and its culture can reveal the presence of urinary system infection and hematuria. In the case of detection of non-infectious leukocyturia, it is necessary to exclude tuberculosis of the urogenital system and associated diseases. In the presence of leukospermia per the results of sperm analysis, it is necessary to carry out a culture study of the ejaculate, a smear from the urethra, mycobacterial culture and serological testing for the presence of viruses. Performing a clinical (general) blood test, coagulogram, reveals hidden blood diseases.

In addition, recent urologic studies or interventions, the presence of episodes of prolonged bleeding or light bruising from minor injuries or surgical interventions, trips to regions where tuberculosis and schistosomiasis are endemic should be considered.

During physical examination of the patient it is recommended to examine the external genital organs, palpate the scrotum for the presence of swelling, elasticity, tuberosity of the testes and appendages, as well as a digital rectal examination to evaluate the prostate for enlargement, elasticity, mobility and nodules. It is also recommended to look for signs of light bruising

or bleeding, such as large bruises (more than 5 cm in diameter) in the absence of injuries and petechiae. It is important to investigate the abdominal cavity for the presence of hepatosplenomegaly, which may indicate major hematologic, hepatic, or infectious diseases. Blood pressure should also be measured to detect hypertension.

Today, per the results of many studies, the link between persistent or recurrent hemospermia and prostate cancer has been proven.
Patients with suspicious lesions detected during rectal examination of the prostate gland, especially those over 50 years of age (over 45 years of age with a family history), need to determine the level of serum prostate specific antigen (PSA).

Performing transrectal ultrasound (TRUS) of the prostate gland allows for a clear visualization of the prostate, seminal vesicles and adjacent structures (detection of calculi, calcinates, cysts, varicose veins of the prostate and inflammatory changes). The effectiveness of this method has been demonstrated in many studies.

If it is impossible to identify pathological changes, while maintaining hemospermia, it is necessary to resort to performing magnetic resonance imaging (MRI) - normal or using an endorectal coil, as well as multispiral computed tomography (MSCT) to better visualize the anatomical and functional state of the pelvic organs.

It is worth noting the fact that in 70–80% of all cases the cause of hemospermia cannot be detected, that is, hemospermia is idiopathic and is of a benign nature of the disease. Nevertheless, on the part of the doctor requires further monitoring of such a patient.

Modern research methods allow to identify the main cause of most cases of hemospermia, and most patients are subject to conservative treatment. But the main goal of the doctor is to eliminate serious life-threatening conditions, such as prostate cancer and bladder cancer, as well as several the diseases already mentioned.

It is necessary to explain to the patient that hematospermia is not always associated with a specific disease. In the case of a single episode of hemospermia in such patients under 40 years of age, further observation is sufficient.

Middle-aged men with recurrent episodes of hematospermia need more careful observation. If an infection is suspected, even with a negative culture, antibiotic therapy may be prescribed as an empirical treatment.

It is worth noting that systemic diseases are to be treated by specialized specialists. Cysts of the prostate or seminal vesicles are aspirated under TRUS control. In the case of recurrent episodes of hemospermia, fibrourethrocystoscopy (expanded veins of the prostate gland and urethral anomalies) can make a big contribution to making the correct diagnosis.

However, in most cases, hemospermia is benign. It is often associated with urogenital infections or inflammatory diseases of the organs of the urogenital system. The changes in the seminal vesicles detected during the examination, and thus the hemospermia that occurs, are often also benign. And if, when detecting hemospermia, there is a suspicion of cancer of the prostate gland or seminal vesicles, an ultrasound transrectal biopsy should be performed.

Thus, the use of modern research methods allows to identify the main cause of most cases of hemospermia. Men with repeated episodes of hemospermia should be constantly monitored by a urologist, since hemospermia can be the first sign of prostate cancer in high-risk groups (men over 45 years of age with a family history, as well as in African-American men).

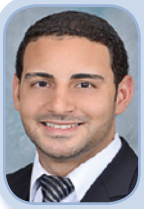
See application form on page 27.

Penile rehabilitation following radical prostatectomy: What do we know so far?

by Run Wang and Jonathan Clavell-Hernandez

Run Wang, MD, FACS
Director of Sexual Medicine
University of Texas McGovern Medical School at Houston and MD Anderson Cancer Center
Houston, TX 77030, USA

run.wang@uth.tmc.edu



Jonathan Clavell-Hernandez, MD
Medical School at Houston and University of Texas MD Anderson Cancer Center
Houston, TX, USA

Radical prostatectomy (RP) techniques have improved in the last few decades. 5-year survival rates after treatment for localized prostate cancer are approximately 98% [1]. Despite its efficacy in treating localized prostate cancer, RP has been shown to have a detrimental effect on patient's erectile function (EF), urinary continence, and hence, the patient's quality of life and general well-being [2,3]. Many urologists believe that we have maximized our techniques for nerve sparing with current technology. Unfortunately, overall, the incidence of erectile dysfunction (ED) after RP is still very high and varies between 14% and 90% [3,4–6]. We need to look for other modalities to improve recovery of EF after prostatectomy.

The concept of penile rehabilitation after RP was proposed in late 1990s. It is based on the understanding of the mechanisms that lead to ED and utilizing different treatment modalities to promote recovery of the male sexual function before and after any insult to the penile erectile physiologic axis [3,7]. It is believed that neuropraxia, ischemic and hypoxic insults, fibrotic remodeling and apoptosis of erectile cells contribute to ED even after meticulous dissection in an attempt to preserve the neurovascular bundle during prostatectomy [3]. Mechanical stretching of cavernous nerves during prostate retraction, thermal injury from electrocautery use, inflammation from surgical trauma and nerve ischemia secondary to blood supply damage, all lead to neuropraxia. Studies have shown that even in the most cautious dissection during nerve-sparing RP, neuropraxia can occur, and it may take up to 3 years for these nerves to recover [8–10]. Lack of erections associated with neuropraxia following RP can itself set up a cascade of harmful processes that negatively affect EF. In 2007, we described the mechanism of how chronic erectile dysfunction promotes hypoxia of the corporeal bodies [8]. Neuropraxia and ligation of the accessory internal pudendal arteries lead to hypoxia and lack of nocturnal erections. This later induces cavernosal fibrosis and transformation of trabecular smooth muscle through collagen, which itself leads to the loss of the veno-occlusive mechanism required to maintain erections. The combination of nerve damage with decreased arterial inflow may exacerbate hypoxia and ultimately result in apoptosis [10].

After understanding these mechanisms, multiple studies have been focused on evaluating ways to increase oxygenation of the cavernosal bodies, decrease tissue fibrosis and apoptosis, and consequently improve EF. Theoretically, the role of penile rehabilitation is to maintain tissue oxygenation and prevent tissue fibrosis until the cavernosal nerves recover from neuropraxia with the return of spontaneous un-assisted tumescence. This is done with daily programmed use of any means to stimulate erectile response. The daily phosphodiesterase 5 inhibitors (PDE5i) logically became the first option due to its ease of use and accessibility. Unfortunately, most randomized controlled trials (RCTs) in last decade and a recent meta-analysis have established the consensus that daily phosphodiesterase 5 inhibitors (PDE5i) does not improve the recovery of spontaneous erections [11–13]. Two of these RCTs were the REINVENT and REACTT trials, both conducted by Montorsi's group. These were multicenter prospective, double-blind, placebo-controlled in which patients with preoperative good erections were randomized into taking PDE5i after surgery. The REINVENT trial evaluated the use of vardenafil, while REACTT assessed the use of tadalafil. Results of the REINVENT trial did not support nightly vardenafil over on-demand dosing and after a wash-out period, no improvement in IIEF score was noted for either protocol when compared to the placebo group [11]. REACTT found that after 9 months of treatment there was a significant difference in reaching the target IIEF-EF ≥22 in the tadalafil once daily group compared to placebo. However, after the drug-free washout period, there was no significant difference in EF between groups with 20.9%, 16.9% and 19.1% of patients reaching target IIEF-EF in the tadalafil once daily, on demand and placebo groups, respectively [12].

These previous trials evaluated the use of PDE5i by relying on self-reported outcomes to determine efficacy of therapy. To exclude the subjectivity of response bias, Kim et al [13] conducted a study in 2016 to evaluate the effects of PDE5i using a more objective approach with a Rigiscan, in addition to the IIEF-EF score. After randomizing 97 patients into taking daily sildenafil with on-demand sildenafil or daily placebo with on-demand sildenafil, the group noted no significant difference in EF between treatment groups based on both IIEF-EF domain scores or RigiScan, therefore suggesting that nightly sildenafil has no benefit over on-demand sildenafil.

Other means of rehabilitation are to use non-oral modalities such as intracavernosal injection therapy, intraurethral alprostadil and vacuum-erection devices (VED). As with oral PDE5i, the use of these modalities has also being disappointing. A meta-analysis confirmed that administration of these modalities can increase EF while the treatment is being used, but once the treatment is discontinued, there was no improvement in recovery of spontaneous EF [14]. Unfortunately, it is difficult to obtain good objective judgement from the available evidence due to limitations in the clinical trials. Most trials evaluated outcomes at one point (less than 12–13 months) which is sub-optimal given that EF has been suggested to take up to 4 years to recover [15]. With these mixed results in clinical studies,

Penile rehabilitation following radical prostatectomy: What do we know so far?

one might wonder why many urologists still offer penile rehabilitation. The answer may rely on the evidence proven in animal and histological data.

RP creates a series of histological alterations in cavernous tissue which include marked increase in collagen fibers along with a decrease of elasticity and smooth muscle cell fibers. Kovanecz et al studied the temporal relationship in the corpora between the expression of inducible nitric oxide synthase, histological and biochemical changes, and the development of corporal veno-occlusive dysfunction after bilateral cavernosal nerve resection (BCNR) [16]. They compared histological penile tissue sections from rats who underwent either BCNR or sham operation and after treating the rats with sildenafil, their results revealed that sildenafil had a myogenic effect on the tissues [16]. These changes with sildenafil were also observed when translated to human subjects. A penile biopsy performed during and 6 months after RP revealed no smooth muscle loss after 6 months in patients taking sildenafil 50 mg and a significant increase of smooth muscle in those taking sildenafil 100 mg ($p<0.05$) [17]. Other animal studies have shown multiple beneficial effects of PDE5i in nerve crush models [8]. PDE5i have been shown to not only promote smooth muscle content, but also ameliorate the fibrotic degeneration normally seen in the corpora cavernosa after BCNR. This occurs through modulation of extracellular matrix and gene expression of tissue growth factors which protect against smooth muscle loss and fibrosis after RP [18]. Other positive effects include decrease in oxidative stress, endothelial cell apoptosis, penile shaft collagen content and hypoxia along with prevention of venous leakage through cGMP-related mechanisms dependent and independent of inducible nitric oxide synthase induction [19, 20]. All these mechanisms, in combination with the neuroprotective effects of PDE5is, have been proven to improve overall erectile function [8].

Another negative impact of RP on sexual function is penile shortening. Savoie and colleagues [21] prospectively measured the penis of 124 men before and at 3-months after RP. Peyronie's disease and patients with history of penile or urethral surgery were excluded. Their results showed that the size of the penis was smaller after RP with a significant difference for flaccid, stretched, pre-pubic fat pad and penile circumference measurements. This led investigators to assess the impact of penile rehabilitation on penile length in the clinical setting and at the molecular level in animal models with bilateral cavernosal nerve injury. The REACTT study clearly showed that penile length loss was significantly reduced with daily tadalafil compared with placebo and on demand groups [12]. Yuan et al. noted that VED therapy preserved EF through anti-hypoxic, antiapoptotic and antifibrotic mechanisms [22]. These findings were later confirmed with penile blood gas analysis which showed an increase in cavernous blood oxygen saturation after VED therapy [23]. The penile tissue and size preservation with VED are proven in multiple randomized and case series clinical trials [24, 25].

Currently, there is no standard treatment algorithm or established clinical guidelines for EF recovery after RP because of controversial evidence related to penile rehabilitation. The controversy of penile rehabilitation will continue until better modalities become available. For now, it is clear that basic scientific studies show that penile rehabilitation programs have a theoretical benefit on EF and clinically proven effect on penile tissue preservation. However, patients should be informed that current rehabilitation programs have not been clinically proven to significantly improve unassisted erections. In our practice, we believe that any rehabilitation is undeniably better than no action at all. We have also noted that patients with high pre-surgery sexual desire, confidence to get and maintain an erection and pre-surgery intercourse satisfaction are the ones who will benefit the most from early rehabilitation after nerve-sparing RP. Given that the current literature lacks irrefutable evidence regarding the effectiveness of penile rehabilitation modalities, there still remains an opportunity for the development of larger trials with sufficiently long-term follow-up to convince the urologic community that penile rehabilitation is inarguably effective.

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Have you read? Best of the best: Clinical research

by Bruno Jorge Pereira

Bruno Jorge Pereira
MD, FEBU, FECSM
Department of Urology
University of Beira Interior (FCS-UBI)
Covilhã, Portugal

brunoalexpereira@gmail.com

Male sexual dysfunction

Stephenson KR, Truong L, Shimazu L. **Why is Impaired sexual function distressing to men? Consequences of impaired male sexual function and their associations with sexual well-being**. J Sex Med 2018; 15: 1336-1349.

The complex association between male sexual function and subjective sexual well-being (sexual satisfaction and distress) may be partially mediated by specific "consequences" of impaired function. This study aimed to pilot a scale assessing consequences of impaired male sexual function in 166 men in sexually active heterosexual relationships, and test whether specific consequences (disruption of sexual activity, negative partner responses) mediated the association between sexual function and well-being. Clinical implications: Sexual consequences represent potential maintaining factors of male sexual dysfunction and may represent key targets of cognitive behavioral treatments.

Baas WR, Butcher MJ, Lwin A et al. **A review of the FAERS data on 5-alpha reductase inhibitors: Implications for post finasteride syndrome.** Urology 2018; 120: 143-149.

To quantify reports made to the FDA Adverse Event Reporting System (FAERS), create a demographic of patient reports, and examine the cluster of symptoms to correlate consistency of post finasteride syndrome (PFS) complaints. PFS is a provisional diagnosis encompassing a cluster of sexual, physical, and psychological and/or neurologic symptoms associated with 5-alpha reductase inhibitor use that emerge or continue after discontinuation of medication. Statistical analysis compared variables of interest between the 2 doses of finasteride (1 mg vs. 5 mg). From FAERS, 2048 monotherapy cases were identified: 1581 of finasteride 1 mg, 240 of finasteride 5 mg, and 226 of unreported doses. Possibly related to labeling changes, from 2011 to 2014, there was a significant increase in adverse events (AEs) reported involving 1 mg dosing. Finasteride use was reported with many sexual AEs including diminished libido, erectile dysfunction, and ejaculatory complaints. Other common AEs included dermatologic, metabolic, and psychological and/or neurologic complaints. FAERS data suggests that finasteride exposure is reported with a diverse collection of symptoms, particularly in younger men on 1 mg dosage compared to older men on 5 mg.

Premature ejaculation

Verze P, Arcaniolo D, Imbimbo C et al. **General and Sex profile of women with partner affected by premature ejaculation: Results of a large observational, non-interventional, cross-sectional, epidemiological study (IPER-F).** Andrology 2018; 6(5): 714-719.

Couple distress is a crucial point in premature ejaculation (PE). PE has been associated with significant bother, inter-personal problems, and dissatisfaction with sexual intercourse for both men and their partners. Adult women aged 18 to 80 years old, sexually active, were randomly sampled from the patient lists of General Practitioners in Italy and were included in this observational, non-interventional, cross-sectional epidemiological study to assess the effect of PE on female sexuality in female partners of men affected from PE and the impact of PE on female sexual quality of life, the presence of sexual problems of the male partner, and to evaluate the prevalence and characteristics of comorbidities.

Subjects were asked to fill: A general questionnaire regarding anthropometric data, lifestyle, marital status, education, occupation, economic conditions, general health status, comorbidities, and sexual habits; SQoL-F, FSDS-R-PE, SDS and SAS questionnaires. In addition, females reported about their partner's ejaculation time and the presence of sexual dysfunctions. Results: A total of 3,104 women were included with a mean age of 45.1 years. Woman with PE partners presented a higher percentage of sexual dysfunction and reported more anxiety compared with female partners of men not affected from PE (42.69 % vs. 20.56 % and 30.95 % vs. 15,34 %, respectively). In addition, they referred more sexual dysfunction in their partners. Hypertension, hypercholesterolemia, arthritis, heart diseases, thyroid disease, a history of menopause, or hysterectomy resulted in significantly more prevalence in women with PE partners. Conclusions: Female partners of PE patients present an increased prevalence of sexual distress, a reduced quality of sexual life, and an increased anxiety score when compared to women whose partners are not affected from PE.

Peyronie's disease

Capece M, Cocci A, Russo G et al. **Collagenase clostridium histolyticum for the treatment of peyronie's disease: A prospective Italian multicentric study.** Andrology 2018; 6(4): 564-567.

Collagenase clostridium histolyticum (CCH) is the first licensed drug for the treatment of PD and is indicated in patients with palpable plaque and curvature deformity of at least 30° of curvature. Only few monocentric studies are available in the current literature and this is the first national multicentric study focusing on CCH injection. In five Italian centers, 135 patients have completed the treatment with three injections fo CCH (0.9 mg) given at 4-weekly intervals in combination to home modelling, stretching and vacuum device using Ralph's shortened modified protocol. An improvement in the angle of curvature was recorded in 94,8 % of the patients by a mean (range) of 19.1 (0–40)° or 42.9 (0–67) % from baseline ($p < 0.001$). There was also a statistically significant improvement in all IIEF and PDQ questionnaires. This prospective multicentric study confirms that the three-injection protocol is effective enough to achieve a good result and to minimize the cost of the treatment.

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Hypogonadism

Defeudis G, Mazzilli R, Gianfrilli D, Lenzi A, Isidori AM. **The CATCH checklist to investigate adult-onset hypogonadism.** Andrology 2018; 6: 665–679

Adult-onset hypogonadism is a syndrome often underdiagnosed, undertreated, or incompletely explored. There are various reasons for this: Firstly, undefined age range of men in whom testosterone levels should be investigated and then no definitive serum cut-off point for the diagnosis of hypogonadism; and finally, variable and non-specific signs and symptoms; men and physicians do not pay adequate attention to sexual health. All these factors make the diagnostic criteria for hypogonadism controversial. The evaluation of the clinical features and causes of this syndrome, its link with age, the role of testosterone and other hormone levels, and the presence of any comorbidities are all useful factors in the investigation of this population. The purpose of this manuscript, after an accurate analysis of current literature, is to facilitate the diagnosis of hypogonadism in men through the use of the CATCH acronym and a checklist to offer a practical diagnostic tool for daily clinical practice. A useful new acronym CATCH (Clinical features and Causes, Age, Testosterone level, Comorbidities, and Hormones) and a practical checklist to facilitate the evaluation of hypogonadism in aging men were developed.

Surgery

Lue TF, Shindel AW. **Five things I wish I would have known earlier in my career: Lessons learned in Peyronie's disease surgery.** J Sex Med 2018; 15(8): 1070-1072.

In this invited commentary the internationally recognized urologist in Peyronie disease (PD) surgery, Tom F. Lue, shares his thoughts on 5 surgical dilemmas from his past several decades: Use of saphenous vein for plaque incision and grafting, management of large calcified or ossified plaques, circumcising vs. longitudinal incisions, management of hourglass deformity and circumferential narrowing and management of residual curvature after penile prosthesis implantation. Tom Lue also proposes the following treatment algorithm for PD: No treatment is recommended in patients for whom penile deformity poses no or minimal bother. Surgery is indicated for large ossified plaques, severe hourglass deformities or indentations with marked hinging, curvatures greater than 90º, and failures of collagenase. All other patients are recommended collagenase injections as a safe and effective first-line therapy for bothersome PD.

Djordjevic ML, Bumbasirevic U, Stojanovic B et al. **Repeated penile girth enhancement with biodegradable scaffolds: Microscopic ultrastructural analysis and surgical benefits.** Asian J Androl. 2018; 20(5): 488-492.

Autologous tissue engineering using biodegradable scaffolds as a carrier is a well-known procedure for penile girth enhancement. We evaluated a group of previously treated patients with the aim to analyze histomorphometric changes after tissue remodeling and to estimate the benefits of repeated procedure. A group of 21 patients, aged 22–37 underwent a repeated penile girth enhancement procedure with biodegradable scaffolds. Procedure included insertion of two poly-lactic-co-glycolic acid scaffolds seeded with laboratory-prepared fibroblasts from scrotal tissue specimens. During this procedure, biopsy specimens of tissue formed after the first surgery were taken for microscopic analysis. The mean follow-up was 38 months. Ultrastructural analysis of these tissue samples discovered the presence of large quantities of collagen fibrils running parallel to each other, forming bundles, with a few widely spread fibroblasts. In total, the mean values of flaccid and erect gain in girth after the second surgery were 1.1 ± 0.4 (range: 0.6–1.7) cm and 1.0 ± 0.3 (range: 0.6–1.5) cm, respectively. Microscopic evaluation of newly formed tissue, induced by autologous tissue engineering using biodegradable scaffolds, showed the presence of vascularized loose connective tissue with an abundance of collagen fibers, fibroblasts, and inflammatory cells, indicating active neovascularization and fibrinogenesis. The benefit of the repeated enhancement procedure was statistically significant.

Jun MS, Gallegos MA, Santucci RA. **Contemporary management of adult-acquired buried penis.** BJU Int 2018; 122(4): 713-715.

The authors present their experience on the buried penis repair technique that includes penile release, tissue resection, wound closure, and penile reconstruction. 73 patients were treated from 2007 to 2017 and were categorized into five stages: Stage 1, involves only a phimotic band; Stage 2, required excision of diseased penile skin with split-thickness skin grafting (STSG); Stage 3, requires scrotal excision; Stage 4, requires escutcheonectomy; and Stage 5, requires panniculectomy. Results: 36 of 73 (49 %) patients had Stage 1–3 disease, whilst 37 of 73 (51 %) were Stage 4–5. There were complications within the first 30 days in 44 of 73 (60 %) patients. In all, 62 of 73 (85%) patients either had no complications or Clavien-Dindo grade I–II complications and nine (12 %) had complications beyond 30 days. Only 5 of 36 (14 %) patients with Stage 1–3 disease had complications. One patient developed recurrent phimosis. Conclusion: Buried penis is a challenging surgical entity where conservative treatment will most likely lead to failure. Surgery is the only means for a lasting cure in these patients and should be used as a first-line treatment. One should expect complications postoperatively, especially within the first 30 days but mostly limited to Clavien-Dindo grade I–II.

Strother MC, Skokan AJ, Sterling ME, et al. **Adult buried penis repair with escutcheonectomy and split-thickness skin grafting**. J Sex Med 2018; 15(8): 1198-1204.

Components of successful buried penis repair include return of directed voiding, elimination of local skin inflammation and infection, improvement in hygiene, return of sexual functioning, cosmesis, and patient satisfaction. The authors describe a technique for surgical correction of adult buried penis, including a technique for skin graft harvesting from the escutcheonectomy

specimen itself, with an emphasis on remaining open questions in the literature. Results: Adult buried penis repair is generally associated with excellent rates of satisfaction and improvement in functioning. Split-thickness skin grafts are associated with excellent rates of successful graft take, even in cases of severe preoperative pathology and patient comorbidity. Although these grafts come at the cost of some increased surgical morbidity, they are associated with low rates of major complications. Morbidity can be further signifcantly decreased by harvesting the graft from the excised escutcheon itself. Conclusion: Surgical correction of adult buried penis is safe and effective.

Hemospermia

Chen R, Wnag L, Sheng X et al. **Transurethral seminal vesiculoscopy for recurrent hemospermia: Experience from 419 cases.** Asian J Androl 2018; 20: 438-441.

Authors summarized their experience in transurethral seminal vesiculoscopy (TSV) for recurrent hemospermia by introducing surgical techniques, intraoperative findings, and treatment outcomes. TSV was performed in 419 patients with an initial diagnosis of persistent hemospermia at Shanghai Changhai Hospital from May 2007 to November 2015. TSV was successfully performed in 381 cases (90.9 %). Hemospermia was alleviated or disappeared in 324 (85.0 %) patients 3 months after surgery. Common intraoperative manifestations were bleeding, obstruction or stenosis, mucosal lesions, and calculus. TSV is an effective and safe procedure in the management of seminal tract disorders. This study may help other surgeons to become familiar with and improve this procedure.

Oncology

Sinnott JA, Brumberg K, Wilson KM et al. **Differential gene expression in prostate tissue according to ejaculation frequency.** Eur Urol. 2018; 74(5): 545-548.

In a prospective study of 31,925 men with 18 yr of follow-up, higher ejaculation frequency (EF) throughout adulthood was associated with lower rates of prostate cancer. To explore this association, authors evaluated whole transcriptome gene expression in the prostate tissue from study participants who developed prostate cancer between 1992 and 2004 (n= 157 tumor tissue, n= 85 adjacent normal). They tested for trends in gene expression according to the level of EF as self-reported in 1992 for ages 20 – 29 yr, 40 – 49 yr, and the year prior to the questionnaire, 1991. There were no associations between EF and gene expression in areas of tumor after accounting for multiple testing. In contrast, in the adjacent normal tissue, 409 genes and 6 pathways were differentially expressed at a false discovery rate <0.2 across categories of EF in 1991. These results suggest that ejaculation affects the expression of genes in the normal prostate tissue. The identified genes and pathways provide potential biological links between EF and prostate tumorigenesis.
Editorial by Dall'Era MA, De Vere White RW. **New insights into ejaculatory frequency and prostate cancer risk: Association, causation, or what do we have to lose?** Eur Urol 2018; 74(5): 549-550.

Jian Z, Ye D, Chen Y, et al. **Sexual activity and risk of prostate cancer: A dose-response meta-analysis.** J Sex Med 2018; 15(9): 1300-1309.

The role of sexual activity (SA) on prostate cancer (PCa) risk is still controversial. This systematic literature search based on PRISMA guidelines was conducted to determine the associations among number of female sexual partners, age at first intercourse, ejaculation frequency (EF), and the risk of PCa. Results: A total of 21 case-control studies and 1 cohort study with 55.490 participants (14.976 patients and 40.514 controls) were included in this meta-analysis. Linear and significant dose-response associations were found among number of female sexual partner as well as age at first intercourse and PCa risk, an increment of 10 female sexual partners associated with a 1.10-fold increase of PCa risk (OR 1.10), and the risk of PCa was decreased by 4 % for every 5-year delay in age at first intercourse (OR 0.96). Although no linear association was observed between EF and the risk of PCa, moderate EF (2 – 4 times per week) was significantly associated with a lower risk of PCa (OR 0.91). Conclusion: Meta-analysis of the included studies indicated that men with fewer sexual partner numbers, older age at first intercourse, and moderate frequent ejaculation were associated with a significantly decreased risk of PCa. Modification of SA factors may appear to be a useful low-risk approach to decrease the risk of PCa.

Female sexual function

Burri A, Buchmeier J, Porst H. **The importance of male ejaculation for female sexual satisfaction and function.** J Sex Med. 2018; 15(11):1600-1608.

Although links between ejaculatory control or intravaginal ejaculatory latency time and female sexual functioning have frequently been reported in the past, no study has investigated the importance of other male ejaculatory characteristics, such as ejaculation volume and intensity, for women's sexuality. This cross-sectional online survey including 240 sexually active heterosexual women using study-specific questions and validated questinnaires aimed to assess the importance of subjectively perceived ejaculation intensity and ejaculation volume for female sexual function and satisfaction. Results: 50.43 % of women considered it very important that the partner ejaculates during intercourse. 18.3 % of women preferred that the partner ejaculates before they reach orgasm, whereas for 53.5 % this did not matter. 22.6 % of women stated that they experienced a more intense orgasm

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when their partner ejaculated during vaginal intercourse. 17.4 % reported that they definitely experienced a more intensive orgasm depending on the intensity of their partner's ejaculation, whereas for 17.8% this did not matter at all. 20.9 % of women did not feel that their orgasm was more intense depending on the subjectively felt ejaculate quantity, whereas the majority (37.9 %) stated that it did not matter. 13.1 % of women regarded the quantity of expelled ejaculate as an expression of their own sexual attractiveness. Women stating that they experienced more intense orgasms when the partner ejaculated, when the partner experienced a more intense ejaculation, and when he expelled a greater ejaculate quantity also reported better lifelong orgasmic function and more lifelong sexual satisfaction. Strength & Limitations: This is the very first study to explore the importance of male ejaculation volume and intensity for women's sexual functioning. Data are of self-report nature and ejaculation characteristics were not objectively measured but by women's self-report. Conclusion: Although male ejaculation and its different aspects seem to play an important role for women, the study demonstrates a considerable variability of women's attitudes toward ejaculatory characteristics.

Illiano E, Mahfouz W, Giannitsas K et al. **Coital incontinence in women with urinary incontinence: An international study.** J Sex Med 2018; 15(10): 1456-1462.

Coital urinary incontinence (CUI) is not much explored during clinical history, and this could lead to an underestimation of the problem. This was a multicenter international study, conducted in Italy, Greece, the United States, and Egypt including sexually active women with UI and in a stable relationship for at least 6 months which intended to evaluate the prevalence and clinical risk factors of CUI in women with urinary incontinence (UI), and to measure the impact of CUI on women's sexuality and quality of life. The UI was classified as stress UI (SUI), urgency UI (UUI), and mixed UI (MUI). 1.041 women (age 52.4 ± 10.7 years) were included. 53.8 % of women had CUI: 8 % at penetration, 35 % during intercourse, 9 % at orgasm, and 48 % during a combination of these. Women with CUI at penetration had a higher prevalence of SUI, women with CUI during intercourse had higher prevalence of MUI with predominant SUI, and women with CUI at orgasm had higher prevalence of UUI and MUI with predominant UUI component. Previous hysterectomy was a risk factor for CUI during any phase, while cesarean delivery was a protective factor. Previous failed anti-UI surgery was a risk factor for CUI during penetration and intercourse, and body mass index >25 kg/m^2 was a risk factor for CUI at intercourse. According to International Consultation on Incontinence questionnaire scores, increased severity of UI positively correlated with CUI, and had a negative impact on the quality and frequency of sexual activity. Clinical Implications: This study should encourage physicians to evaluate the CUI; in fact, it is an under-estimated clinical problem, but with a negative impact on quality of life. Conclusion: CUI is a symptom that can affect sexual life and should be investigated during counseling in all patients who are referred to urogynecological centers.

Sexual behavior

Carvalho J, Czop O, Rocha M, Nobre P, Soares S. **Gender differences in the automatic attention to romantic vs. sexually explicit stimuli.** J Sex Med 2018; 15(8): 1083-1092.

Gender differences in sexual responses and cognitive and emotional processing to romantic and sexually explicit stimuli have been reported. However, these differences seem to depend on the automaticity of the task that is being used, thus suggesting that gender differences may be the result of specific mechanisms rather than a generalized effect. This study included 26 women and 30 men, heterosexual, in which romantic and sexually explicit stimuli were presented as distractors while a concurrent letter discrimination task was performed, followed by a self-report task assessing subjective sexual and emotional responses to the stimuli and aimed to investigate gender differences on automatic attention to sexual stimuli, and to test its relationship with sexual excitation proneness. Findings revealed that sexually explicit pictures yielded more automatic attention capture. However, this effect was superseded by pornography consumption, which likely reflects a habituation mechanism. Also, data revealed gender-x type of picture interaction effects only at the self-report task, with men rating sexually explicit stimuli as more sexually exciting, and women rating these stimuli as less pleasant. No relationship was found between automatic attention proxies and sexual excitation proneness. Clinical translation: While therapeutic strategies are used as tools to improve attention to sexual stimuli (and, hence, increase sexual arousal), the current findings suggest that the specific pathways by which attention influences sexual response are still to be established. Also, gender differences on the subjective appraisal of sex stimuli suggest that therapeutic approaches, consisting on exposure techniques, must recognize gender specificities. Conclusion: Whereas both genders do not seem to differ in automatic attention toward romantic and sexually explicit stimuli, their responses do differ in their subjective appraisal of the stimuli.

Have you read? Best of the best: Basic research

by Nuno Louro

Nuno Louro, MD
Department of Urology
Hospital of Porto
University of Porto
Porto, Portugal

nunorlouro@gmail.com

Female sexual dysfunction

Zhang H, Liu T, Zhou Z et al. mi-R137 **Affects vaginal lubrication in female sexual dysfunction by targeting Aquaporin-2.** Sex Med. 2018; 6(4): 339-347

Female sexual arousal disorders are very common worldwide but are rarely the subject of basic investigation. The pathophysiology of vaginal lubrication is poorly understood. As the last barrier of vaginal lubrication, epithelial tissue is responsible for the transport and rematching of ions, water, and other molecules that play an important role in the formation of vaginal lubricants. Therefore, the role of fluid transport in vaginal lubrication has attracted increasing attention. It has been suggested that microRNAs (miRNAs) play an important role in the regulation of fluid transport. By comparing vaginal samples obtained from 15 women with lubrication disorder and 15 women with normal function, the authors screened differentially expressed miRNAs in women with and without vaginal lubrication disorder by microarray analysis and they found that miR-137 was highly expressed in the vaginal epithelial tissues of women with lubrication problems. Additionally, functional studies in vitro validated the important role of miR-137 in the modulation of vaginal epithelial cell water permeability. They suggested that the overexpression of miR-137 might downregulate the expression of aquaporin-2 (AQP2), a key protein in fluid transport in vaginal epithelial cells. Decreased expression of AQP2 in vaginal epithelial cells may lead to impaired vaginal epithelial fluid transport capacity, thus inhibiting the secretion of vaginal lubricant, resulting in vaginal lubrication disorders. If confirmed in larger samples and in vivo, AQP2 could be manipulated as a therapeutic target against lubrication disorder and its sexual consequences.

Erectile dysfunction

Assaly R, Gorny D, Compangnie S, et al. **The favorable effect of empagliflozin on erectile function in an experimental model of type 2 diabetes.** J Sex Med. 2018; 15(9): 1224-1234

Erectile dysfunction is very common in men with Type 2 Diabetes (T2DM), and this is a well-known difficult-to-treat group of patients. Specific sodium/glucose cotransporteur 2 inhibitors (SGLT-2Is), which are approved for the treatment of T2DM, regulate blood glucose levels by blocking the re-uptake of filtered glucose in the proximal tubule of the kidney, leading to excretion of glucose via the urine. The EMPA-REG Outcome trial results showed that empagliflozin (a SGLT-2I) reduces the cardiovascular and renovascular complications in patients with T2DM. In this study the authors investigated the effects of empagliflozin on ED in a T2DM rat model (male Goto-Kakizaki). 48 GK rats were randomly assigned to 2 experimental groups where they were fed ad libitum over 4 weeks with regular diet or medicated diet (regular diet pre-mixed with empagliflozin) and also compared to age-matched Wistar rats, fed with regular diet. The in vivo effect of empagliflozin on erectile function was assessed by electrical stimulation of the cavernous nerve at different frequencies under anesthesia in the presence or absence of acute intravenous injection of sildenafil. Endothelium-dependent, independent, and nitrergic relaxations of cavernosal strips from the rats were studied. The results showed a beneficial effect of chronic empagliflozin in erectile function, and although the potential mechanism could not be elucidated, it could be associated with an improvement in the impaired diabetes-induced nitrergic relaxations of the corpus cavernosum in GK rats and partly attributable to an attenuation of the diabetes-related inflammation state. It would be very interesting to investigate if this positive effect is also seen in humans.

Nunes KP, de Oliveira AA, Szasz T, et al. **Blockade of toll-like receptor 4 attenuates erectile dysfunction in diabetic rats.** J Sex Med. 2018; 15(9): 1235-1245

An emerging body of evidence suggests that toll-like receptor (TLR4), an important component of the innate immunity, mediates vascular dysfunction. The hypothesis that the TLR4 pathway participates in the development and maintenance of vascular pathologies has gathered wide support but, despite advancement in the understanding of TLR4 signaling transduction, the precise model of interaction between this receptor with its ligands is still a debatable issue. This group has previously demonstrated that TLR4 activation contributes to diabetic bladder dysfunction and hypertension-associated ED. In the current study, the authors aimed at determining not only if TLR4 regulates penile vascular tone but also whether this receptor mediates ED in vivo in a rodent model of diabetes. Streptozotocin-induced diabetic rats received a daily intraperitoneal injection of an anti-TLR4 antibody. Control animals (CTL) were injected with vehicle alone. Additionally, cavernosal strips were acutely incubated for 30 minutes with CLI-095, a TLR4 inhibitor. Functional studies, Western blotting, erectile function, immunohistochemistry, and biochemical analyses were performed. The results suggest that penile tissue from diabetic rats have higher TLR4 density compared to CTL animals. Functional experiments revealed that the sensitivity to phenylephrine (PE) in diabetic penile tissue decreases not only with the chronic treat-

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ment (anti-TLR4 antibody) but also with acute blockade of TLR4 (CLI-095). The cavernosal relaxation induced by EFS in tissue precontracted with PE in diabetic rats treated with an anti-TLR4 antibody or after incubation with CLI-095 was also significantly increased compared to nontreated diabetic animals. Also, higher levels of superoxide were found in corpus cavernosum of diabetic compared to normoglycemic rats, and TLR4 blockade was able to partly prevent this effect. Similarly, nitrite levels, a widely used indirect method to measure nitric oxide, found in lower levels in the diabetic cavernosal tissue was enhanced by treatment with an anti-TLR4 antibody. Taking into consideration these results and the current literature, the authors speculate that activation of TLR4 downstream pathways in the penis due to hyperglycemia may contribute to deficient cavernosal relaxation by possibly affecting the NO-mediated cGMP levels. These findings open research avenues for new ED treatments in the presence of diabetes.

Musicki B, Bhunia AK, Karakus S, Burnett AL. **S-nitrosylation of NOS pathway mediators in the penis contributes to cavernous nerve injury-induced erectile dysfunction.** Int J Impot Res. 2018; 30(3); 108-116

Despite advances in surgical techniques such as nerve-sparing, erectile dysfunction (ED) is still a very common consequence of radical prostatectomy. This complication is mainly associated with cavernous nerve injury with effects observed in the penis at cellular and molecular levels. NO signaling in the penis is mediated through a well recognized signal transduction pathway involving activation of soluble guanylyl cyclase (sGC) and 3,5-cyclic guanosine monophosphate (cGMP)-induced activation of protein kinase G (PKG). It is increasingly recognized that NO signaling is also mediated by S-nitrosylation, an alternative signaling pathway for NO that mediates cGMP-independent effects. This group recently demonstrated the importance of transnitrosylation mechanisms in the penis in physiologic NO signaling, such that unchecked nitrosylation decreases NO bioactivity and increases oxidative/nitrosative stress. Whether S-nitrosylation is involved in pathologic effects in the penis and exerts deleterious effects with respect to erection preservation under conditions of penile neuropathy is unknown. In the current investigation they used a rat model of cavernous nerve crush injury (BCNI) vs rats submitted to sham surgery. Rats were randomly divided into four groups (n = 9–12/group): Sham + Vehicle, Sham + N-acetyl-cysteine (NAC), BCNI + Vehicle, and BCNI + NAC. NAC, an antioxidant and a denitrosylating agent was given to rats in drinking water starting 2 days before BCNI or sham injury and continuing for 2 weeks after the surgery. After assessment of erectile function (intracavernous pressure), penes were collected for measurements of S-nitrosylation by Saville–Griess and TMT-switch assays and PKG-I function by immunoblotting of phospho(P)-VASP-Ser-239. The results showed that ED under conditions of penile neuropathy induced by cavernous nerve injury is mediated in part by S-nitrosylation of eNOS and its downstream signaling mediator sGC and also that denitrosylation in the face of cavernous nerve injury may protect erectile function by preserving NOS signaling pathway function. This novel mechanism for the derangement of NO signaling pathway that promotes ED under conditions of cavernous nerve injury opens new and interesting paths of investigation.

Premature ejaculation

Xia JD, Chen J, Yang BB, et al. **Differences in sympathetic nervous system activity and nmda receptor levels within the hypothalamic paraventricular nucleus in rats with differential ejaculatory behaviour.** Asian J Androl. 2018; 20(4): 355-359

Lifelong premature ejaculation is a very common sexual dysfunction and has been defined as a neurobiological disorder. The data collected so far indicate that ejaculation is predominantly mediated by a spinal control center, which is in turn influenced by the descending inhibitory and excitatory supraspinal sites in the brainstem, hypothalamus and preoptic area. Many types of neurotransmitter with inhibitory or excitatory roles, such as serotonin, dopamine, adrenaline, acetylcholine, norepinephrine, oxytocin, gamma-aminobutyric acid, N-methyl-D-aspartic acid (NMDA), and nitric oxide, have been implicated in the central regulation of ejaculation reflex. This group had recently found that NMDA receptors in the paraventricular nucleus of the hypothalamus (PVN) facilitate ejaculation by enhancing sympathetic nervous system (SNS) activity. In the present study, in an experimental rat model, they found that male rats with differential ejaculatory behavior had different SNS sensitivities, which correlated with NMDA receptor levels in the PVN, and this supports different levels of NMDA receptors in the PVN as contributing to changes in ejaculatory latency during sexual activity. They demonstrated that the density of NMDA receptors in the PVN distinguished between three groups (sluggish, normal and rapid ejaculators), with the density being the highest in "rapid" ejaculators. This further supports the model of a neurobiological disorder, opening some potential news routes to pharmacological interventions.

Peyronie's disease

Mateus M, Ilg MM, Stebedds WJ, et al. **Understanding the role of adenosine receptors in the myofibroblast transformation in peyronie's disease**

Peyronie's disease (PD) is a fibrotic disorder characterized by the formation of plaques within the tunica albuginea (TA) of the penis with a poorly understood etiology (which probably accounts for the lack of an effective medical treatment). This fibrotic disorder is characterized by the expression of several cytokines and growth factors, fibrin deposi-

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tion, and myofibroblast differentiation with an increased myofibroblast activity, resulting in increased extra-cellular matrix (ECM) protein production and eventual plaque formation, suggesting a pivotal role for myofibroblasts in the pathophysiology of PD. Several studies have shown that adenosine receptors play different roles in acute and chronic injuries and have been suggested to promote fibrosis in several organs. Adenosine and adenosine receptors have been studied in other fibrotic diseases but scarcely in PD. In order to investigate the role of adenosine receptors in myofibroblast transformation in PD, the authors isolated fibroblasts from the non-PD TA tissue and PD plaque tissue and were transformed into myofibroblasts using transforming growth factor (TGF)-β1. Quantification of α-smooth muscle actin and adenosine receptors (adenosine receptor A1 [ADORA1], adenosine receptor A2A, adenosine receptor A2B [ADORA2B], and adenosine receptor A3) was performed using immune cytochemistry, in-cell enzyme-linked immuno-sorbent assay (ICE), and real-time reverse transcription quantitative polymerase chain reaction. The effect of various adenosine receptor agonists or antagonists on TGF-β1-induced myofibroblast transformation was measured using ICE. The experiments showed that the protein and messenger RNA levels of α-smooth muscle actin in non-PD TA cells and PD plaque-derived cells were significantly higher in cells exposed to TGF-β1 than those not treated with TGF-β1 and that 2 of 4 adenosine receptors (ADORA1 and ADORA2B) were found to be expressed in both cell populations. Among various adenosine receptor agonists/antagonist investigated, only ADORA2B agonist, BAY 60-6583, significantly inhibited myofibroblast transformation in a concentration-dependent manner when applied simultaneously with TGF-β1. The authors concluded that ADORA2B agonists may be a novel potential therapeutic target for PD if applied during early, non-stable phase of PD.

Mohede DCJ, de Jong IJ, Bank RA, van Driel MF. **Verteporfin as a medical treatment in Peyronie's disease.** Sex Med. 2018; 6(4): 302-308

Verteporfin is registered in the United States and Europe as a sensitizer for photodynamic therapy to eradicate abnormal blood vessels in the eye associated with the wet form of macular degeneration. VP accumulates in the abnormal blood vessels. When stimulated by non-thermal red light (wavelength 693 nm) in the presence of oxygen, VP produces reactive short-lived singlet oxygen and other oxygen radicals, locally damaging the endothelium and resulting in blockage of these vessels. Research showed that VP decreased expression of fibrotic genes in fibroblasts collected from nodules of patients suffering from Dupuytren's disease, plausibly by de-activating transcription in the Yes Activated Protein (YAP) pathway. It has also been shown that inactive VP attenuates renal fibrosis in mice subjected to unilateral ureteral obstruction, probably by blocking the transcriptional activation of targets in the YAP cascade involved in fibrosis-related processes. The objective of the present study was to determine whether VP would have similar effects on (myo)fibroblasts derived from plaques in patients with Peyronie's Disease (PD). The authors took biopsies, at the time of surgery for PD, from the plaque in 5 patients. To confirm the pathologic phenotype of cells isolated from PD plaques, baseline immunofluorescent stainings were performed that showed considerable levels of α-SMA, being a marker for the presence of myofibroblasts. The mRNA ratios of all the genes related to fibrosis except YAP decreased significantly after treatment with VP within 24 and 48 hours. These results suggest inhibition of fibrosis in the YAP cascade, downstream of YAP and that VP might benefit patients mostly in the acute phase of PD, but possibly also in the chronic phase.

MEETINGS AND EVENTS CALENDAR 2019

Dr. Roberto Larocca
Urology Unit
University Federico II
of Naples, Italy

robertolarocca87@gmail.com

Janauary 2019

Joint ISSM-SASSM Session at the Annual Congress of the Urological Society of India (USI)
23 – 26 January, 2019
Bhubaneswar, Odisha, India

March 2019

ISSWSH/ISSM Joint Meeting 2019
7 – 10 March 2019
Atlanta, GA, USA
www.isswshissm2019.org

34th Annual EAU Congress 2019
15 – 19 March 2019
Barcelona, Spain
https://eaucongress.uroweb.org

May 2019

Annual Congress of the American Urology Association (AUA) 2019
3 – 7 May 2019
Chicago, IL, USA
http://www.aua2019.org/

October 2019

24th Congress of the World Association for Sexual Health
12 – 15 October 2019
Mexico City, Mexico
www.was2019.org

2019 Annual Fall Scientific Meeting of SMSNA
24 – 27 October 2019
Nashville, TN, USA
www.smsna.org/V1/meetings/20th-annual-fall-scientific-meeting-of-smsna

November 2019

SLAMS Annual Meeting 2019
14 – 16 November 2019
Sao Paulo, Brazil
www.slamsnet.org

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