



ESSM TODAY

European Society for Sexual Medicine

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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

IMPRINT

Publisher: ESSM
Editor-in-Chief: Ferdinando Fusco, Italy
Layout: MCI Germany

www.essm.org



Ferdinando Fusco, MD, PhD
Editor-in-Chief

Welcome Address

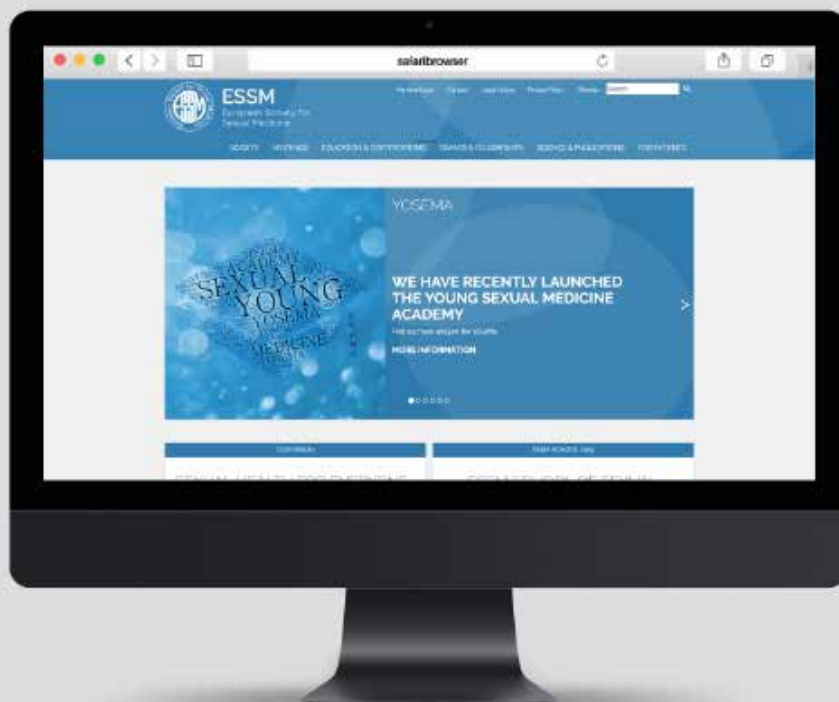
DEAR ESSM MEMBER, DEAR FRIEND,

this summer issue of ESSM TODAY exhibits to all ESSM members a brand new look to admire.

At the age of 25, the European Society of Sexual Medicine is in the full of its maturity, and its colours start to change toward sunny, full ripe chromatic nuances. Our society is recognized more and more as a referral society for sexual medicine by many professionals of varied cultural origin and intellectual background worldwide, and is even more proud of its multidisciplinary and international scope. Scientific update, certified medical, surgical and psychosexual training, cultural exchange in the fields of sexual medicine in European countries and beyond: ESSM is all of this and much more. Being a member of ESSM means for you to be part of the widest and valuable network in the world of sexual medicine, where links are strongest than boundaries, and this is possible thank to your participation.

So let me thank you on behalf of the European Society of Sexual Medicine for your contribution to our common development! We are sure we will continue to grow up and improve to fulfil more and more the needs and desires of our members.

It will be great to meet you in Prague at the next annual meeting!



Visit us on www.essm.org



Ondřej Trojan

TH klinika, Karlovo namesti No. 379/3
Nove Mesto, 120 00 Praha 2
Prague, Czech Republic

Facts

1921

First state-run Sexological Institute was founded at the Charles University in Prague

1950's

Kurt Freund invented penile plethysmography

INDEPENDENT MEDICAL BRANCH

The Czech Republic is one of the few countries where sexology is acknowledged as an independent medical branch and where physicians can obtain a professional degree in the field

EDUCATIONAL PROGRAM

ESSM School of Sexual Medicine aiming at training of young colleagues

PRAGUE IS FAMOUS FOR

Beautiful architecture, beer* and Czech food.

*FUN FACT:

Czechs consume the most beer per capita in the world. You can go join them for a Pilsner-style larger (*their most famous brew*) in any old alluring pub – called a hospoda – around town.

Why should you come to Prague? – A welcome to Prague by the local chair

DEAR COLLEAGUES,

It is not only an honour, but also a great pleasure for me to serve as your host for the upcoming 22. Congress of the European Society for Sexual Medicine. The city of Prague is known for its beauty, rich history and as well as for its perfect location in the heart of Europe. The city attracts more than a million of tourists yearly. One could say that if not anything else, this would be enough for the nomination to host such an event. But actually -there is much more!

Prague is a city where the first state-run Sexological Institute was founded at the Charles University in 1921 and it has been running until now. Prague was the place where Kurt Freund invented penile plethysmography in the late 1950's. The Czech Republic is one of the few countries where sexology is acknowledged as an independent medical branch and where physicians can obtain a professional degree in the field. But not only history plays the role! Current research focusing on brain research / fMRI in paraphiliac and normal objects is one of the most promising projects carried out at the National Institute of Mental Health.

Not to be forgotten - the educational program of ESSM School of Sexual Medicine aiming at training of young colleagues and intensifying the knowledge of advanced colleagues will organize its 3-days-long preparation course before the Congress, crowned with final exams on the first congress day.

Our local organizing committee, which I proudly chair, will do maximum to help organizers in reaching the highest possible level of the scientific meeting. The location is perfect and Prague Congress Centre allows organizing up-to-date plenary sessions, workshops, focused meetings in smaller groups, and various other modalities as well as poster presentations or exhibitions, all of that in warm and welcoming atmosphere, although January can be sometimes frosty. The scientific level is of course very much depending on the approach of you, members of the ESSM. That's why I would like to encourage all of you to start working on your active presentation meeting high standards of our Society because without your participation the meeting can't be really successful.

But sincerely: isn't that a perfect idea to come to Prague after the Christmas/Hanukkah busy time and after the New Year hangover and to enjoy sexual science and to breathe the history bewitched in charming old city at the same time? I guess it is! There are plenty of pubs, restaurants, bars, cafés, and other locations where one can relax after a day dedicated to science. Not a bad idea to take a few more days off after or prior to the event and explore the town in depth or even travel around the small, but beautiful, and very safe Czech Republic. And last but not least: Best beer available almost everywhere!

Ondřej Trojan

In behalf of Czech Society for Sexual Medicine

Utility of doppler ultrasound in Peyronie's disease



Javier Romero-Otero

Hospital Universitario 12 Octubre
HM Hospitales



Borja García Gomez

Hospital Universitario 12 Octubre
HM Hospitales

HISTORIC FEATURES

The use of ultrasound in the diagnosis of Peyronie's disease (PD) was first described by Alteffar and Jordan in a paper published in 1981. They concluded that this technique was useful to demonstrate the plaque itself and its calcification, allowing to identify those patients who will benefit from a medical or surgical treatment.

But it was not until 1991, when Lopez and Jarow described the utility of the duplex ultrasound in the assessment of PD patients. They found evidence of arterial disease in 27 % of the so called "impotent" patients and plaque in only 39 % of the whole group.

Since then, ultrasound has been used in men with PD to localize lesions, follow plaque size, and perform Doppler vascular studies. Among men who are diagnosed with PD but do not have palpable plaques, penile ultrasound is often demonstrative of septal fibrosis, intracavernosal fibrosis, or sub-tunical calcifications. Studies have evaluated the prevalence of calcification in chronic PD and used the presence of calcified plaques as an exclusion criterion for studies of medical treatment of PD.

The current guidelines recommendations

However, nowadays, for the main clinical practice guidelines the duplex ultrasound does not appear to be particularly relevant or to play a significant role in the diagnostic evaluation of patients with PD.

Thereby, the EAU Guidelines on Erectile Dysfunction, Premature Ejaculation, Penile Curvature and Priapism, in the 2019 edition, establish that "ultrasound measurement of the plaque's size is inaccurate and operator dependent" (level of evidence -LE- 3), and that "doppler ultrasound is required to ascertain vascular parameters associated with ED (LE 2a). They recommend not to use ultrasound measurement of plaque size in everyday clinical practice (weak). The AUA Guidelines on PD, 2015 version, give an expert opinion recommendation in this situation, in which "clinicians should perform an in-office intracavernosal injection test prior to invasive intervention, with or without duplex doppler Ultrasound". In contrast, the Evidence-Based Management Guidelines on Peyronie's Disease of the European Society for Sexual Medicine, establish that the penile color duplex ultrasonography (CDU) provides a safe, low-cost, and rapid means of objectively characterizing PD, with a LE 3 and a grade recommendation C.

The lack of good quality evidence in the literature may explain the weak recommendations given in these guidelines. But at the same time, many groups may not be using the doppler ultrasound routinely precisely because these recommendations, with concerns about the real utility of this technique in the assessment of patients with PD.

In recent years, and along with the change in the management of this disease, there has been an increasing evidence to support the routine use of the penile doppler ultrasound in the evaluation of these patients.

THE IMPORTANCE OF CALCIFICATION

Besides the confirmation of the presence of a plaque, the description of tunica albuginea thickening (>2 mm for most groups, >3mm for some) and its localization, ultrasound can be easily used to evaluate the calcification of the plaque.

In 2008 Bekos et al. published a prospective series including 95 patients with PD in different stages. They were all classified according to ultrasonographic patterns ("solitary hyperechoic lesions without acoustic shadow (group A), moderately hyperechoic multiple scattered calcified lesions with acoustic shadows (group B), dense calcified hyperechoic plaques with acoustic shadow (group C)"), and were included in a watchful waiting protocol. Ultrasound was repeated after 1 year. 9 of 11 patients in group A (81.8 %) saw a slight improvement, while the 2 other patients developed calcifications. Both the groups B and C saw a progression of the disease with more calcifications and curvature worsening, concluding that patients with "solitary hyperechoic lesions without acoustic shadow" may see a spontaneous resolution or improvement of their affection.

In 2009, Smith et al published the ultrasound findings in a large cohort of 528 patients with PD. They found that any kind of calcification was present in 31.4 % of them, and that other important findings when planning surgery, as septal fibrosis and intracavernosal fibrosis, were present in 6.8 % and 15 % of the patients, respectively. they concluded that ultrasound may help track the evolution of the condition in individual patients and in the future may be useful for tailoring treatment strategies.

This way, the same group published one year later a retrospective study of a cohort of 518 PD patients, in which they found a progression to surgery rate of 25 % after an average follow-up of 1.25 years. Patients who underwent surgery were more likely to have subtunical calcifications present at the first clinic visit (OR 1.75), but no other of the sonographic characteristics analyzed (tunical thickening, septal or intracavernosal fibrosis) were associated with progression. These findings stood unvariable even after adjustment for age, marital status and PD specific characteristics (duration of symptoms, degree of curvature, penile deformity, penetration difficulty, loss of penile length, ability to have intercourse and treatment for PD before enrolment in study).

These findings were confirmed by another paper by Levine et al, in which they analyzed retrospectively a cohort of 1041 patients with PD. 34 % of them presented with any kind of calcification, and they were graded in 3 different groups: grade 1 (calcification <0.3 cm), grade 2 (>0.3 cm, but <1.5 cm), grade 3 (>1.5 cm; or ≥ 2 plaques >1.0 cm). Men with grade 3 penile calcification had an increased likelihood of progression to surgical intervention, and a higher likelihood of undergoing a grafting procedure.

Since the approval of the collagenase of the Clostridium histolyticum (CCH; Xiapex®, Swedish Orphan Biovitrum AB, Stockholm, Sweden; Xiaflex®, Endo Pharmaceuticals, Malvern, PA, USA) for the treatment of PD, knowing the status of calcification of the plaque seems to have an increasing importance, as two papers published in 2018 demonstrate. The first, by Wymer et al. is a prospective series of 192 patients with PD who underwent treatment with CCH, and in whom a Doppler ultrasound was performed before and after treatment. Noncalcified plaque (OR 2.50; $p=0.03$) and curvature $\geq 60^\circ$ (OR 5.01; $p=0.02$) were found to be significant predictors of $\geq 20\%$ improvement in composite curvature. When differentiated by calcification severity, those with no calcification achieved significant improvements in curvature (28.1° vs 10.3° , $p=0.04$), compared to moderate (shadowing) or severe (>1 cm).

The second study, by Cocci et al. enrolled 135 patients with PD into a prospective multicentre single-arm. They built a nomogram able to predict treatment success after CCH. When analysing factors associated with penile curvature improvement after treatment, the found that baseline curvature (OR 1.14; $p<0.01$), basal

plaque (OR 64.27; $p<0.01$), low calcification (OR 0.06; $p<0.01$) and high calcification (OR 0.03; $p<0.01$) were significant predictors of curvature improvement. They concluded that patients with longer PD duration, greater baseline curvature and basal plaque location had a greater chance of treatment success, whereas any kind of calcification was associated with poor response. Vascular assessment of the penis

When combined with an intracavernous injection of an erectogenic medication (e.g. alprostadil), doppler ultrasound may be used to assess penile vascularization along with a direct inspection of the penile malformation (Kelami test). Both end diastolic velocity (EDV) and peak systolic flow (PSF) need to be measured 10 and 20 minutes after a standard administration of 10 μg of alprostadil. Although the measures considered normal may vary depending on the group, is usually defined as a PSV >25 cm/s and a EDV <5 cm/s. In case of an arterial insufficiency, the PSF will be <25 cm/s with normal EDV; and in case of venous leakage, the EDV will be >5 cm/s with a normal PSF.

It is known that when planning a grafting technique to solve PD, the older patients and specially those with cardiovascular risk factors, are more likely to develop and erectile dysfunction after surgery, so they may be offered penile prosthesis implantation with modelling of the fibrous plaque. Doppler ultrasound may help identify more accurately these patients at risk, so counseling should be more efficient.

IN CONCLUSION

Better description of plaque's characteristics, specially the degree of calcification, seems to be of great importance to understand the potential development of the disease and to optimize and personalize the subsequent treatment. The recent introduction of CCH as a conservative therapy for this disease strengthens this statement. Besides, knowing the vascular status of the penis with PD may help to counsel adequately the patient in the best surgical approach to avoid complications.

Doppler ultrasound is a relatively low-cost and minimally invasive technique can quickly and efficiently identify these factors. So, for the authors, there are sufficient reasons to routinely perform a doppler ultrasound of the penis in the assessment of patients with PD, at least before planning the better treatment to receive.



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Including regularly updated scientific material, monthly updated literature reviews, the most recent guidelines, lecture recordings and presentations from past ESSM congresses), the opportunity to participate in the ESSM educational programs, and to apply for scientific and support grants and a reduced fee for the ESSM annual congress.

ESSM Annual Membership Fees

(January to December)

Combined ESSM/ISSM Fee <i>incl. JSM Journal</i>	160 €
ESSM only Fee	50 €
ESSM only Residents in Training Fee*	25 €

**available against proof of evidence*

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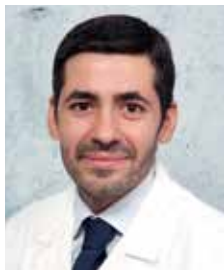
Foto von Artem Beliaikin von Pexels

The role of penile rehabilitation after radical prostatectomy: where are we today and what perspectives do we have?



Nicolò Schifano

Università Vita-Salute San Raffaele,
Milan, Italy



Paolo Capogrosso

Università Vita-Salute San Raffaele,
Milan, Italy
Unit of Urology; URI; IRCCS Ospedale
San Raffaele, Milan, Italy

Radical prostatectomy (RP) is still considered the treatment of choice in most cases of clinically localized prostate cancer (PCa), allowing for excellent oncological outcomes¹. Although many advances have been made in both understanding prostate anatomy and in minimally invasive surgery, the occurrence of erectile dysfunction (ED) after RP remains a common adverse event negatively impacting on patients' quality of life. Current series report postoperative ED rates ranging between 19 and 78 %². This wide variations in the erectile function (EF) outcomes largely depends on different applied definitions of postoperative ED and on differences in the baseline characteristics of included patients. If we look at data from the Prostate Testing for Cancer and Treatment (ProtecT) trial³-randomizing PCa patients to either RP, active monitoring or radiation therapy, the EF outcomes after surgery are even less encouraging: at baseline, prior to RP, 67 % of men reported levels of erections which were firm enough for intercourse, but in the prostatectomy group at the 6-month follow up this rate fell to 12 %. Erectile function remained worse in the prostatectomy group at all time points. Over the last decades, PCa has been more and more often diagnosed at an earlier stage⁴; as a consequence patients has been diagnosed at younger ages, hence the increased importance of focusing on post-operative sexual function. Erectile dysfunction after RP is mainly attributed to neurovascular bundle trauma, which cannot be completely avoided even with the best nerve-sparing techniques⁵. Indeed, ED becomes clinically evident immediately after surgery, owing to a temporary damage of the cavernous nerves called neuropraxia. This results in a reduction of both daily and nightly erections and is associated with persistent levels of cavernous tissue hypoxia⁶. In vitro and in vivo data support the idea that penile hypoxia could prompt collagen accumulation, smooth-muscle apoptosis and fibrosis. All of these could lead to irreversible ED. Conversely, EF may return gradually after surgery, although it can take approximately 2 years or longer⁷ and with only a fraction of patients able to recover their baseline EF.

PENILE REHABILITATION AFTER SURGERY

Penile rehabilitation has been proposed as a strategy to stimulate the recovery of EF after surgery for PCa. The concept of penile rehabilitation, first suggested by Montorsi et al.⁸ in the late 1990s, is based on the use of any treatment/management approach aiming at preserving the EF through the improvement of cavernosal oxygenation to both maintain proper endothelial function and prevent smooth-muscle fibrosis. Several treatment protocols have been proposed over time to enhance EF recovery after surgery: the most common approaches of penile rehabilitation include the use of oral phosphodiesterase type 5 inhibitors (PDE5is); vacuum erection device (VED); intra-cavernous injection (ICI) therapy; or a combination of them⁶. Tal et al.⁹ analyzed penile rehabilitation practice patterns among American Urological Association (AUA) members and found that penile rehabilitation strategies were adopted in 89 % of cases after RP, with PDE5is being the preferred option, followed by VED and ICI.

DOES PENILE REHABILITATION ACTUALLY WORK?

Several randomized control studies (RCTs) tried to answer this question by testing the efficacy of different oral PDE5is in promoting the recovery of unassisted erections in men treated with RP. Padma-Nathan et al.¹⁰ randomized 76 patients to receive either nightly sildenafil or placebo for 36 weeks after RP. After an 8-week drug-free period they observed better level of unassisted EF among patients treated with sildenafil. However, the encouraging findings of this first trial have not been further replicated: Pavlovich et al.¹¹ comparing nightly vs on-demand sildenafil did not find any significant improvement in terms of unassisted EF recovery after surgery. Similarly, in a double-blind RCT, Montorsi et al.¹² reported data assessing the effect of on-demand vs nightly vardenafil 10 mg: after a 2-month drug washout period, EF recovery rates did not significantly improve in either vardenafil group. Likewise in a large RCT¹³ comparing tadalafil 5 mg once daily vs. on demand vs. placebo, the authors found no EF differences between the two active treatments groups as compared to the the placebo arm, after

a 6-week drug-free period. Overall, the investigators concluded that although tadalafil could not “rehabilitate” (i.e. promoting the onset of drug-unassisted EF recovery after RP), on demand dosing could still be considered to maintain the cavernosal tissue integrity levels. Those findings were further confirmed by Mulhall et al.¹⁴ showing that early treatment with daily tadalafil had no effect on unassisted EF recovery at 9 months after treatment cessation. Summarizing, although PDE5is can improve post-operative sexual function, the available level 1 data fail to clearly demonstrate an improvement in the chance of recovering spontaneous unassisted erections with PDE5is treatment after RP. To date, consistent with most influential uro-andrological (AU, AUA, ESSM) guidelines, the advantage of any specific molecule or any penile rehabilitation protocol over the others has not been demonstrated.

DO WE HAVE TO LOOK BACKWARDS?

Intracavernous injection with alprostadil was the first proposed protocol to enhance EF recovery after RP. This treatment has been associated with high and immediate levels of effectiveness, especially in terms of penile hardness. Montorsi et al.⁸ reported data of 27 post-RP patients who were submitted to intracavernous injections (ICIs) of PGE1, 2-3 times per week. At 6-month follow up, 67 % of treated men showed levels of recovered EF, compared to only 20 % in the control group. Similarly, Mulhall et al.¹⁵ showed that performing ICIs 3 times per week after RP could lead to a 52 % return of functional erection at 18 months follow-up as compared to only 19 % in the control group. However, ICIs have been historically associated with low patients compliance: in their series Polito et al.¹⁶ observed that out of 430 patients who were offered a protocol of postoperative ICIs for sexual rehabilitation, 157 (36.5 %) refused to enter the protocol, and 18.6 % dropped out of treatment over the first 6 months.

DO WE HAVE TO LOOK FORWARD?

In light of this data physicians may be more prone to look for novel rehabilitating strategies. Currently, few innovative treatments aimed to improve EF recovery after RP are under investigation in both preclinical and clinical studies. Low-intensity extracorporeal shock wave therapy (LI-SWT) is a novel

treatment modality which facilitates the occurrence of cellular microtrauma, which in turn stimulates the release of angiogenic factors and the eventual neo-vascularization of the treated tissue. Li et al.¹⁷ tested the effect and mechanisms of LI-SWT in a rat ED model induced by pelvic neurovascular injury. The authors showed that LI-SWT was able to promote a significant improvement in terms of nerve bundles compared to sham treatment, as assessed with immunofluorescence staining of neurofilaments. Moreover an enhanced dedifferentiation and proliferation of Schwann cells in the dorsal nerve of the penis was also observed. In a similar animal model, Wang et al.¹⁸ showed that LI-SWT was able to ameliorate the negative functional and histologic effects of severe pelvic neurovascular injury. To date, two clinical studies have investigated the effect of LI-SWT in the post-operative setting. Zewin et al.¹⁹ reported data of 128 post nerve-sparing radical cystoprostatectomy subjects. All patients were allocated to one of three groups: LI-SWT; PDE5i; and control. During the follow-up, 16 % more patients in the LI-SWT group showed satisfactory EF recovery levels as compared to the control group. Although the difference was not statistically significant ($p=0.14$), the finding was still considered of clinical relevance. In a second study, Frey et al.²⁰ reported data of 16 patients with mild to severe ED after 12 months since RP. All patients were treated with a 6-week course of LI-SWT and then re-assessed at 1- and 12-month after treatment with no other erectogenic aids allowed during the study period. Results showed a significant improvement in terms of EF recovery, as assessed with the IIEF-EF. As the authors correctly pointed out, it is possible that even better results could be achieved if the treatment is given at an earlier stage after surgery, thus preventing penile fibrosis.

One of the most promising strategies in post-RP penile rehabilitation setting is represented by the intracavernous injection of bone marrow-mononuclear cells (BM-MNCs). Following a range of preclinical encouraging results, a few phase 1 and 2 clinical trials are currently ongoing²¹. The BM-MNCs are a heterogeneous population of cells, which include mesenchymal stem cells, endothelial progenitor cells, and haematopoietic stem cells. These progenitor cells may exert anti-apoptotic, neurotrophic, and angiogenic effects. You et al.²² selected 12 post-RP patients with localized PCa and whose ED had

proved to be unresponsive to medical treatments. Patients were divided into four groups and were treated with escalating BM-MNC dosages. Compared to baseline levels, a significant improvement in terms of intercourse satisfaction and EF were observed at the 6-month follow up. Interestingly, clinical benefits were also associated with improvement of peak systolic velocity at the level of the cavernous arteries and with increased penile nitric oxide release.

A last and less-investigated novel treatment for restoring EF after RP is the intracavernous treatment with Platelet-rich plasma (PRP). The PRP is autologous blood plasma that contains platelet concentrations exceeding physiological standards by 3-7 times. This is obtained through multiple blood centrifugations. The PRP has been used in many branches of medicine for several decades, including cosmetology, ophthalmology, sports medicine, cardiology, trauma surgery, plastic surgery, tissue engineering, restoration of nerves, and treatment of type 2 diabetes mellitus complications²³. Hence, it has been argued that the angiogenic, vasculogenic and regenerative effects of PRP could be useful to treat ED. Matz et al.²⁴ reported data of 17 patients treated with PRP who were assessed with the International Index of Erectile Function (IIEF-5) questionnaire. The IIEF-5 scores improved by an average of 4.14 points after PRP therapy, with minor adverse effects. Despite PRP potential, Epifanova et al.²³ recently suggested that the effectiveness of PRP treatment should be interpreted with caution, because of the lack of placebo-controlled studies and of the small sample size of published trials.

CONCLUSIONS

Despite the improvements in surgical techniques and post-operative management strategies, ED is still commonly observed after RP. Promising results with novel treatment modalities has been recently reported in both preclinical and small clinical studies. The preliminary findings of LI-SWT, PRP, and BM-MNCs appear exciting. However, available data are currently insufficient to draw definitive conclusions. Further large, placebo-controlled, multicenter trials should be encouraged to overcome the current existing gap in the setting of ED treatment after RP.

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Bruno Jorge Pereira

Urology Department of Centro Hospitalar e Universitário Cova da Beira (CHUCB) And Health Sciences Faculty of the University of Beira Interior (FCS-UBI) Covilhã, Portugal

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SURGERY

Herbert K, Kohler TS. Acute Post-Inflatable Penile Prosthesis Glans Ischemia: Review of Incidence, Pathophysiology, and Management Recommendations. J Sex Med 2019; 16: 1–4.

In this invited commentary Kevin Herbert and Tobi Kohler provide a review of incidence, pathophysiology, presurgical considerations, and management recommendations for glans ischemia immediately after IPP implantation. The rarity of glans ischemia, combined with the disastrous permanent damage, likely produced a significantly underreported complication (fewer than 25 cases). Surgeons managing post-IPP glans ischemia must understand that they are not deciding between conservative or surgical management but rather when they will perform surgical management. Immediate removal of the device markedly increases the likelihood of glans salvage, whereas delaying device explantation will almost certainly be at the expense of tissue loss. "When in doubt, take it out!"

Neuville P, Morel-Journel N, Cabelguenne D, et al. First Outcomes of the ZSI 475 FtM, a Specific Prosthesis Designed for Phalloplasty. J Sex Med 2019; 16: 316–322.

The ZSI 475FtM is a new prosthesis that has recently been specifically designed for phalloplasty. It has several functions that have been conceived to answer the challenges of implantation after phalloplasty: a large base for pubic bone fixation, realistically shaped hard glans, and a pump shaped like a testicle. Surgical outcomes were analyzed after implantation of the prosthesis between June 2016 and September 2017 (single institution, single surgeon). 20 patients who had gender dysphoria and underwent operation for a female-to-male procedure were included. The mean age was 37.9 years. Complications after 21 implantations included 2 (9.5 %) infections that were medically treated (Clavien II), 1 (4.7 %) infection treated by explantation (Clavien IIIb), 2 (9.5 %) mechanical failures (Clavien IIIb), and 1 (4.7 %) malpositioning (Clavien IIIb). The mean follow-up was 8.9 months (SD 4.0), with 50 % of the implanted patients having >12 months of follow-up. 14 patients (70 %) answered the satisfaction questionnaire. 12 patients (85.7 %) had regular penetrative sexual intercourse. The mean IIEF-5 score was 20.2 of 25, the mean Self-Esteem and

Relationship score was 84.5 of 100, and the mean Erectile Dysfunction Inventory of Treatment Satisfaction score was 82 of 100. 13 patients (92.8 %) were satisfied or very satisfied with the prosthesis. This new innovative prosthesis could better answer the challenges faced by the implantation of an erectile device by phalloplasty. Preliminary results for the ZSI 475 FtM are encouraging. Safety seems to be satisfactory, and patient satisfaction is high.

Le BV, McVary KT, McKenna K, et al. Use of Magnetic Induction to Activate a "Touchless" Shape Memory Alloy Implantable Penile Prosthesis. J Sex Med 2019; 16: 596–601.

A novel physiologic penile prosthesis that uses shape memory alloy properties to mimic the transition between a flaccid and erect penis using magnetic induction instead of hydraulic pressure is described. The authors prototyped an implantable penile prosthesis cylinder using temperature-tuned nickel titanium alloy tubes laser cut to specifications. The device was then tested implanted in an animal tissue model and in cadaveric tissue. Testing consisted of placing the device deactivated in its more malleable and compressed state, then activating it using an external inducer wand while measuring temperature changes that occur on the surface of the device, within the tissue, and at the skin surface. Using a handheld magnetic inductor, the SMA penile prosthesis was successfully activated with no direct contact under 45 seconds. This handheld wand produced a magnetic field that penetrated tissue and caused the appropriate phase change within the prosthesis. The fully activated device resisted buckling forces of 2.66 kgf ± 0.045. This non-hydraulic shape memory prosthesis obviates the needs for reservoirs and pumps, and the wand-based interaction with the device may be easier to use. It appears to show thermal safety in controlled environments, however real-world use would need further studies. In conclusion, a shape memory penile prosthesis is a promising alternative to hydraulic-based penile prostheses and can be activated safely and efficiently using magnetic induction in our models of the human penis.

MALE CARDIOVASCULAR HEALTH

Isiozor NM, Kunutsor SK, Laukkanen T, Kauhanen J and Laukkanen JA. Marriage Dissatisfaction and the Risk of Sudden Cardiac Death Among Men. *Am J Cardiol* 2019; 123: 7–11.

Conflicts in marriage have been associated with potential risk of cardiovascular disease; however, there is lack of prospective evidence on the association between marriage satisfaction and sudden cardiac death (SCD). The authors of this study aimed to assess the association between perceived level of marriage satisfaction and risk of SCD. This study employed the Kuopio Ischemic Heart Disease study, an ongoing prospective population-based study in Finland. Perceived level of marriage satisfaction was assessed in 2,262 men using a well-structured self-administered questionnaire. During a median follow-up period of 25.9 years, 239 SCDs were recorded. The mean age of participants was 53 (SD 5.2) years. On adjustment for several conventional cardiovascular risk factors, hazard ratio (95 % CI) of SCD was 1.90 (CI 1.09 to 3.32; $p = 0.02$) for men who were dissatisfied with their marriage, compared with men who were satisfied with their marriage. The association remained consistent on further adjustment for preexisting coronary heart disease, socioeconomic status, and years of education 1.86 (CI 1.07 to 3.25; $p = 0.03$). In conclusion, middle-aged Caucasian men who are dissatisfied in their marriages should be regarded as a high-risk group when compared with men in very satisfied marriages, independent of conventional cardiovascular risk factors.

ERECTILE FUNCTION

Limoncin E, Gravina GL, Lotti F et al. The Masturbation Erection Index (MEI): Validation of a New Psychometric Tool, Derived from the Six-Item Version of the International Index of Erectile Function (IIEF-6) and from the Erection Hardness Score (EHS), for Measuring Erectile Function During Masturbation. *BJU Int.* 2019 Mar; 123(3): 530–537.

To validate a psychometric instrument, the Masturbation Erection Index (MEI) able to evaluate erectile function (EF) during masturbation. In fact, although the evaluation of EF during masturbation is pivotal in evaluating erectile dysfunction (ED), to date no specific psychometric tools have been developed to measure it both in the routine clinical practice and in the

experimental setting. 99 men with ED were compared 102 sexually healthy men. All the men were requested to complete both the six-item version of the International Index of Erectile Function (IIEF-6) and the MEI. Internal consistency of the MEI was >0.93 . Test-retest reliability was 0.982 (95 % confidence interval [CI] 0.975–0.987). Bland-Altman analysis showed a good level of agreement between the IIEF-6 and MEI in the whole ED population, with stronger agreement in the organic-ED subpopulation. The estimated area under the curve of the MEI was 0.983 ($P < 0.001$; 95 % CI 0.954–0.996), with a score of ≤ 27 as the optimal threshold to discriminate between the presence and absence of ED during self-induced masturbation. In conclusion, MEI showed good internal consistency and a good level of agreement with the IIEF-6. Hence, the MEI fulfills the major psychometric requirements for measuring EF during masturbation.

Foy CG, Newman JC, Berlowitz DR, et al. Blood Pressure, Sexual Activity, and Erectile Function in Hypertensive Men: Baseline Findings from the Systolic Blood Pressure Intervention Trial (SPRINT). *J Sex Med* 2019; 16: 235–247.

Erectile function, an important aspect of quality of life, is gaining increased research and clinical attention in older men with hypertension. This study aimed to assess the cross-sectional association between blood pressure measures (systolic blood pressure [SBP]; diastolic blood pressure [DBP]; and pulse pressure [PP]) and (i) sexual activity and (ii) erectile function in hypertensive men. 1,255 male participants in a larger randomized clinical trial of 9,361 men and women with hypertension aged >50 years were analyzed. 857 participants (68.3 %) reported being sexually active during the previous 4 weeks. The mean (SD) IIEF-5 score for sexually active participants was 18.0 (5.8), and 59.9 % of the sample reported an IIEF-5 score <21 , suggesting erectile dysfunction (ED). In adjusted logistic regression models, neither SBP nor DBP was significantly associated with sexual activity. In multivariable linear regression analyses in sexually active participants, lower SBP and higher DBP were associated with better erectile function. In additional multivariable analyses, lower PP pressure was associated with better erectile function. Erectile dysfunction was highly prevalent in this sample of men with hypertension, and SBP, DBP, and PP were associated with erectile function in this sample. Blood pressure is an important consideration in the assessment of erectile

function in men with hypertension.

ERECTILE DYSFUNCTION

Grubbs JB, Gola M. Is Pornography Use Related to Erectile Functioning? Results From Cross-Sectional and Latent Growth Curve Analyses. *J Sex Med* 2019; 16: 111–125.

Despite evidence to the contrary, a number of advocacy and self-help groups persist in claiming that internet pornography use is driving an epidemic of erectile dysfunction (ED). This work sought to explore whether mere pornography use itself and self-reported problematic use of pornography are related to ED, both cross-sectionally and longitudinally. A series of 3 samples of sexually active men who also used pornography were collected. Across all 3 samples, there was evidence of a positive, cross-sectional association between self-reported problematic use and ED, but no consistent association between mere use itself and ED. These results suggest that among non-treatment-seeking pornography users, self-reported problematic use likely is associated with concurrent reports of ED, but that the links between these variables are not directional or causal in nature.

Rhim HC, Kim MS, Park Y-J, et al. The Potential Role of Arginine Supplements on Erectile Dysfunction: A Systemic Review and Meta-Analysis. *J Sex Med* 2019; 16: 223–234

This meta-analysis aimed to assess the efficacy and safety of arginine supplements in erectile dysfunction (ED). Studies compared arginine supplements with placebo or no treatment, focusing only on patients with mild to moderate severity of ED. In total, 10 randomized controlled trials met the inclusion criteria, reporting the outcomes of 540 patients with ED. The analysis demonstrated that arginine supplements with dosage ranging from 1,500 to 5,000 mg significantly improved ED compared with placebo or no treatment. Arginine supplements also caused significant improvements in the IIEF subdomain scores of overall satisfaction, intercourse satisfaction, orgasmic function, and erectile function, whereas the IIEF sexual desire score remain unchanged. The results of this systematic review and meta-analysis provide evidence on the effectiveness of arginine supplements for mild to moderate ED.

PEYRONIE'S DISEASE

Moncada I, Krishnappa P, Romero J, Torremade J et al. Penile Traction Therapy with the New Device 'Penimaster PRO' is Effective and Safe in the Stable Phase of Peyronie's Disease: A Controlled Multicentre Study. BJU Int. 2019; 123(4): 694–702.

To evaluate the efficacy and safety of a new penile traction device (PTD) in a group of patients with stable Peyronie's disease (PD) compared with a non-intervention group in a multicentre study. A total of 93 patients with chronic stable PD (without erectile dysfunction, with no significant pain, and with a unidirectional curvature of at least 45° being stable for > 3 months) were recruited and followed for a 12-week period. Of these patients, 47 were randomly assigned to the PTD group (PG) and 46 to the non-intervention group (NIG). Patients were asked to apply the PTD 3–8 h a day for 12 consecutive weeks, with specific instructions regarding the progressive increase of traction force applied to the penis over time. The primary outcome of the study was the change in the degree of curvature measured in the fully erect state after intracavernosal injection of alprostadil at baseline, 1, 2 and 3 months. 41 patients in the PG and 39 in the NIG completed the study. There was an overall reduction in curvature of 31.2° ($P < 0.001$) at 12 weeks compared to baseline in the PG, representing a 41.1 % improvement from baseline, which significantly correlated with the number of daily hours the device was applied in a dose-dependent manner. Those patients using the device < 4 h/day experienced a reduction of 15°–25° (mean 19.7°, 28.8 % improvement; $P < 0.05$), while patients using the device > 6 h/day experienced greater curvature reduction, ranging from 20° to 50° (mean of 38.4°, 51.4 % improvement; $P < 0.001$). In contrast, no significant changes in curvature were observed in the NIG. Mild AEs occurred in 43 % of patients, such as local discomfort and glans numbness. In conclusion, the use of the PTD, a non-invasive treatment, should be offered to patients with stable PD for 3 consecutive months before performing any corrective surgery, as this provided a significant reduction in the curvature, an increase in penile length and a significant improvement of the symptoms and bother induced by PD.

PENILE FRACTURE

Rodriguez D, Li K, Apoj M, et al. Epidemiology of Penile Fractures in United States Emergency Departments: Access to Care Disparities May Lead to Suboptimal Outcomes. J Sex Med 2019; 16: 248–256.

The epidemiology of penile fractures in the emergency setting is not well described. Authors have examined the incidence, evaluation, management, risk factors predicting surgical repair or hospital transfer, and use of financial resources in patients presenting with penile fractures to the emergency departments (ED) nationwide in the United States. ED visits with a primary diagnosis of penile fractures between 2010–2014 were abstracted from the Nationwide Emergency Department Sample. 8,029 ED visits for penile fracture in the US were observed, which represents a national incidence of 1.02 per 100,000 male subjects per year. 63.9 % were treated non-surgically or discharged from the ED, 25.7 % underwent surgical repair, and 10.3 % were transferred to other institutions. Hospital factors which predicted surgical repair included Northeast region, teaching hospital status, trauma hospital status, high volume ED, and urban location. Clinical risk factors which predicted surgical repair included hypertension, smoking, alcohol dependence, drug abuse, erectile dysfunction, hematuria, urethral injury, and urinary retention. Factors leading to patient transfers included non-academic, rural and non-trauma hospitals, low economic income and low emergency department volume. In addition, weekend and spring presentation were associated with higher transfer rates, while summer presentation was associated with surgical repair. Clinical Implications: A large proportion of penile fractures are discharged from the ED, indicating possible health care access disparity. In conclusion, this large retrospective study of penile fractures in the US ED setting demonstrates a stable incidence of penile fractures presenting to the US emergency departments. A quarter of patients undergo immediate surgical repair, 10 % are transferred to other institutions and 63.9 % of patients are discharged home. The high proportion of ED discharges may be due to access to health care disparities.

ONCOSEXUALITY

Capogrosso P, Vertosick EA, Benfante NE et al. Are We Improving Erectile Function Recovery After Radical Prostatectomy? Analysis of Patients Treated over the Last Decade. Eur Urol. 2019; 75(2): 221–228.

The last decade has seen several advances in radical prostatectomy (RP) technique and post-RP care that are relevant to erectile function (EF) recovery. The authors examined whether these practice changes have led to observed improvements in EF rates over time. 2364 patients treated with either open or minimally-invasive RP at a single academic center in 2008–2015. To mitigate confounding by the surgical learning curve, only patients treated by surgeons who performed at least 100 procedures were considered. EF before and after RP was assessed by IIEF-6, with recovery defined as IIEF-6 ≥ 24. EF recovery rates of patients treated with bilateral nerve-sparing surgery and free from adjuvant/salvage treatment at the time of EF assessment were analyzed. A significant decrease over time of the EF recovery rates at both 12 and 24 mo post-RP (all $p = 0.01$) was observed. In conclusion, findings from a high-volume center suggest that, despite the advancements in surgical and postoperative care, EF outcomes after RP have not improved over the last decade. Additional strategies are required to improve EF recovery after RP.

Nascimento B, Miranda EP, Jenkins LC, et al. Testosterone Recovery Profiles After Cessation of Androgen Deprivation Therapy for Prostate Cancer. J Sex Med 2019; 16: 872–879.

Androgen deprivation therapy (ADT) is frequently used in the treatment of prostate cancer worldwide. Variable testosterone (T) recovery profiles after ADT cessation have been cited. Serum early morning total T (TT) levels, collected at baseline and periodically after ADT cessation, were analyzed. Patient age, baseline T level, duration of ADT, and presence of diabetes and sleep apnea were selected as potential predictors of T recovery. 307 men with a mean age of 65 ± 8 years were included. Mean duration of ADT was 17 ± 25 months, and median follow-up was 31 ± 35 months. Mean TT values were 379 ng/dL at baseline and 321 ng/dL at >24 months. At 24 months after cessation of ADT, 8 % of men

remained at castrate level, 76 % returned to TT >300 ng/dL, and 51 % had returned back to baseline. Lower baseline T levels (TT < 400 ng/dL) and ADT duration >6 months were associated with a lower likelihood of recovery to normal TT at 24 months. Age >65 years and receiving ADT for >6 months were significantly associated with a slower T recovery. T recovery after ADT is not certain and may take longer than expected. T recovery rates after ADT cessation vary according to patient age, ADT duration, and baseline T levels. Approximately one-quarter of patients failed to normalize their TT level, and one-tenth of men remained at castrate levels 24 months after ADT cessation. Considering the range of side effects of low T, these findings must be discussed with patients before initiating such therapies.

Almont T, Bouhnik A-D, Charif AB, et al. Sexual Health Problems and Discussion in Colorectal Cancer Patients Two Years After Diagnosis: A National Cross-Sectional Study. J Sex Med 2019; 16: 96–110.

Colorectal cancer (CRC) is accompanied by specific treatment-related physical (ostomy, incontinence) and psychosexual (body image, depression) consequences on sexual health. This study aimed to assess sexual health of patients from a French

nationwide longitudinal study with CRC 2 years after diagnosis (n=487, 258 men and 229 women, 77 % colon cancer and 23 % rectal cancer). Overall, 54 % of patients reported a decrease in sexual desire, 61 % a decrease in frequency of intercourse, and 48 % a decrease in the possibility to reach an orgasm. Patients with rectal cancer had significantly more frequent troubles with desire and orgasm than did patients with colon cancer. Patients still experiencing fecal incontinence 2 years after diagnosis had decreases in all sexual desire, intercourse, orgasm, and satisfaction. Regarding the discussion about sexuality, only 20 % of men, 11 % of women, 11 % of patients with colon cancer, and 33 % of patients with rectal cancer recalled having discussed sexuality with the medical team. Factors independently increasing the chance to have discussed sexuality with the medical team were younger age, having an ostomy, and radiotherapy. This study highlights the lack of discussion about sexuality with the oncology team and the need for specific sexual rehabilitation interventions, especially for patients with rectal cancer and fecal incontinence. Developing these aspects may help patients with CRC improve their sexual prognosis.

DESIRE

Bolmont M, Bianchi-Demicheli F, Boisgontier MP, et al. The Woman's Body (Not the Man's One) Is Used to Evaluate Sexual Desire: An Eye-Tracking Study of Automatic Visual Attention. J Sex Med 2019; 16: 195–202.

Vision of the human body has been shown to be key in eliciting sexual desire. However, whether the visual pattern characterizing sexual desire is different in women and men is still unclear. Heterosexual healthy women and men (n=106) were tested on a picture-viewing task associated with eye tracking. The context of sexual desire was activated by asking the participant whether they perceived such desire while looking at sensual pictures of heterosexual couples. 2 areas of interest were created to investigate visual patterns (face vs. body area). Results showed longer fixations on body rather than face areas irrespective of participant gender. Moreover, all participants looked longer at women's than men's bodies and at the faces of the opposite sex. These findings confirm the association between the human body and sexual desire. They also reveal the unique attentional attractiveness of woman's bodies across genders.

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Nuno Louro

Urology Department of Centro Hospitalar e Universitário do Porto (CHUP),
University of Porto (ICBAS-UP)
Porto, Portugal

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FEMALE SEXUAL DYSFUNCTION

Alvisi S, Baldassarre M, Gava G, et al. Structure of Epithelial and Stromal Compartments of Vulvar and Vaginal Tissue From Women With Vulvo-Vaginal Atrophy Taking Ospemifene. J Sex Med 2018. 15: 1776–1784.

The morphological and physiological changes in vulvar and vaginal epithelium of menopausal women lead to a number of symptoms including sexual dysfunction and low quality of life. Selective estrogen receptor modulators (SERM) have proven effective to reduce vulvo-vaginal atrophy (VVA) symptoms. Ospemifene is the only SERM approved by the Food and Drug Administration and European Medicines Agency for the treatment of moderate to severe VVA in menopausal women and has been proved to restore the vaginal epithelium characteristics of post-menopausal women. In this study the authors wanted to extend current knowledge on the effects of ospemifene at vestibular level and to provide direct evidence of its impact on collagen content and composition at vaginal and vulvar epithelium levels. They included 20 women 50 to 80 years of age with the diagnosis of physiological menopause and without evidence of significant co-morbidities. Eleven women were taking ospemifene for at least one month, and 9, the control group, were not. Full-thickness tissue biopsies of the proximal and distal anterior vaginal wall and from the left and right vulvar vestibulum were taken for evaluation of histological features, glycogen content, total collagen and collagen type I/III ratio. They have shown that the effects of ospemifene extend to the vulvar vestibule, with growth and maturation of the epithelium. They have also shown an increase in the total collagen content in women taking ospemifene and a significantly increased collagen Type I/III ratio in their vaginal epithelium. These results should be confirmed in a larger sample of women under a prospective randomized design so that matched comparisons before and after therapy can be performed.

Caruso S, Cianci A, Cianci S, et al. Ultrastructural Study of Clitoral Cavernous Tissue and Clitoral Blood Flow From Type 1 Diabetic Premenopausal Women on Phosphodiesterase-5 Inhibitor. J Sex Med 2019. 16: 375–382.

Neurovascular factors, due to diabetes, can impair vulvar, clitoral and vaginal flow, contributing to sexual arousal disorder

in diabetic women. Phosphodiesterase type 5 (PDE5) inhibitors are the first line of treatment in men with erectile dysfunction but are still struggling to find their place (if any) in the treatment of female sexual dysfunction. The current study aimed to evaluate the effects of PDE5 inhibitors on the in vivo histomorphologic structure of the clitoral cavernosal tissue of premenopausal type 1 diabetic women. They enrolled 38 women in a prospective randomized study, of which 28 completed the trial (13 taking tadalafil 5 mg daily and 15 in the control group). The women underwent microbiopsy of the clitoral body during surgical therapy of a benign gynecological pathology and the tissue was processed for electron microscopy. Translabial colour doppler ultrasound was used to measure the peak systolic velocity (PSV), the end diastolic velocity (EDV) and the pulsatility index (PI) of clitoral arteries. The investigation showed that diabetic women had ultrastructural abnormalities of smooth muscle cells (SMC) and that women on PDE5 inhibitors had a larger mean SMC thickness than women without drug intake. These changes correlated with colour-flow Doppler sonography – a better clitoral flow was recorded in women on PDE5 inhibitor. One of the important limitations of this study is the fact that sexual function of these women was not investigated, so it is impossible to correlate the findings with sexual behaviour. Nevertheless these data could suggest that a daily treatment (rather than on demand) could be a better approach for diabetic women with organic sexual dysfunction.

ERECTILE DYSFUNCTION

Yang BB, Hong ZW, Zhang Z, et al. Epalrestat, an Aldose Reductase Inhibitor, Restores Erectile Function in Streptozocin-induced Diabetic Rats. Int J Impot Res; 2019. 31: 97–104

Erectile dysfunction is very common in men with diabetes. Several pathologic processes can contribute to sexual dysfunction in this group but peripheral neuropathy is one of the most relevant. One of the proposed mechanisms of neural injury is the increasing of the polyol pathways with accumulation of sorbitol. The subsequent depletion of myoinositol reduces Na/KATPase activity, causing diabetic neuropathy. Epalrestat is an aldose reductase (AR) inhibitor, the rate-limiting enzyme of the polyol pathway. It has been approved to human use, improving the

declined function of peripheral nerves and increasing the diameter of nerve fibres of diabetic patients. In this study the authors aimed to investigate if epalrestat could restore the erectile function of diabetic erectile dysfunction, using a rat model (diabetic streptozocin-induced). They gave intragastric epalrestat daily to a group of ten rats, and saline to other 10 (the control group). They assessed erectile function by measuring intracavernous pressure (ICP) and the ratio of the ICP/mean systemic arterial pressure (MAP). The levels of AR, nerve growth factor (NGF) neuronal nitric oxide synthase (nNOS), α -smooth muscle antigen (α -SMA) and vonWillebrand factor (vWF) were also measured. Epalrestat partly restored ICP and increased the ICP/MAP ratio. The content of α -SMA-positive smooth muscle cells and v-WF-positive endothelial cells in the corpora cavernosa was decreased in diabetic rats and was partly restored after treatment with epalrestat. The treated rats also had a higher expression of NGF and n-NOS. It would be very interesting to see if these effects are also seen in the human corpus cavernosum, a dose-response validation and translation into a clinical trial.

Campbell JD, Alenezi H, DeYoung L, et al. Hydro-Jet Dissection of the Cavernous Nerves Preserves Erection Function in a Radical Prostatectomy Animal Model. J Sex Med. 2019; 7; 104–10

Many factors affect rerecovery of erectile function after radical prostatectomy (RP) for prostate cancer, including preoperative function, age, the degree of nerve-sparing (NS) during surgery and the need for adjuvant treatment. Several maneuvers used during NS-RP can have a negative impact on erectile function (electrothermal injury, excessive traction, transection or devascularization of the cavernous nerves (CN). Hydro-jet dissection (HJD) technology involves the application of a thin high-pressure fluid stream to establish and expand surgical planes. It has already been used in NS-RP with mixed results and the authors of this article state that before supporting HJD as an acceptable alternative to current NS approaches, preclinical studies must elucidate a mechanistic and functional benefit. With that objective they designed this study, using 32 male Sprague-Dawley rats that were randomized to 4 groups: sham surgery, bilateral HJD of CN, blunt CN injury or stretch CN injury. After 4 weeks, erectile function was assessed by measuring intracavernous pressure (ICP), and penile tissues were

harvested for immunohistologic studies. The HJD group had a higher mean peak and more sustainable rise in ICP than the other dissection groups and erectile function returned to baseline function in the HJD group, suggesting that this technique has minimal impact on the CN. They also noticed preservation of both α -SMA and n-NOS after HJD, demonstrating the potential neuroprotective role of this technology. It has already been proved that this technique is safe in humans but there's a need to prove its erectile function protective role in well designed human studies.

Nunes da Silva C, Pedrosa Nunes K, De Marco Almeida F, et al. PnPP-19 Peptide Restores Erectile Function in Hypertensive and Diabetic Animals Through Intravenous and Topical Administration. J Sex Med. 2019; 16: 365–74.

Peptides from animal venoms, such as some arthropods including spiders, can cause priapism. One example is the toxin PnTx2-6, renamed δ -CNTX-Pn2a from the spider Phoneutria nigriventer, which improves erection in normotensive, hypertensive, and diabetic animals, although it is extremely toxic and induces many side effects such as edema, vascular congestion, cellular necrosis, nuclear condensation, or cytoplasmic vacuolation in the heart, lungs, kidneys, liver, and brain. The modeled structure of δ -CNTX-Pn2a enabled the design of a 19-amino acid synthetic peptide that this group named Phoneutria nigriventer potentiator peptide (PnPP-19). PnPP-19 improves the erectile function, apparently without eliciting side effects, showing low immunogenicity and no signs of toxicity. The aim of this study was to evaluate the efficacy of PnPP-19 in hypertensive and diabetic mouse/rat models in restoring erectile function, after topical administration; verify the biodistribution of PnPP-19 administration (topical and intravenous), permeation, and cyclic guanosine monophosphate (cGMP)/nitric oxide via implication. Corpus cavernosum relaxation was evaluated using cavernous strips from male spontaneous hypertensive rats (SHR) and from streptozotocin (STZ)-diabetic mice contracted with phenylephrine and submitted to electrical field stimulation before and after incubation with PnPP-19 (108 mol/L, 10 minutes) or vehicle. This procedure was also used to determine cGMP/nitric oxide levels, at 8 Hz and to check the effect of PnPP-19 with sildenafil citrate. Biodistribution assays were

performed using iodine 123-radiolabeled PnPP-19. In vivo erectile function was evaluated using intracavernous pressure/main arterial pressure (ICP/MAP) ratio in STZ-diabetic rats after PnPP-19 topical administration. Their results suggest that PnPP-19 improves the erectile function in hypertensive and diabetic animals, because it relaxed corpus cavernosum strips from hypertensive (SHR) rats and from STZ diabetic mice and rats, independent of PDE5 inhibition, besides increasing the ratio ICP/MAP in SD rats. The concomitant treatment with sildenafil suggests an additive beneficial effect. These results support the idea of this peptide as a possible new drug to treat ED and the announced clinical studies in humans are awaited.

HYPOGONADISM

Lee DS, Choi JB, Sohn DW. Impact of Sleep Deprivation on the Hypothalamic-Pituitary-Gonadal Axis and Erectile Tissue. J Sex Med. 2019; 16: 5–16.

Sleep deprivation (SD) is a common problem in modern society and it has been implicated in several pathophysiological processes in the human organism. However, the effect of SD on sex-related hormones has not yet been well explained. SD has been shown to activate many stress-related pathways, including the hypothalamic-pituitary-adrenal axis. In addition, testosterone (T) contributes to the intracellular signalling pathway in erectile tissue, and low T levels can lead to penile tissue degeneration. Thus, if SD induces low T levels, these could exert a negative influence on the cavernosal tissue in terms of oxidative stress. The authors investigated the target in the HPG axis that is mainly affected by SD and whether the subsequent SD-induced reduction in T levels was responsible for triggering oxidative stress in the cavernosal tissue. They used 56 male Wistar rats for this experiment. First, 16 rats were subjected to 72 hours of SD, and the following were compared with 16 control rats: (i) levels of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), and cortisol; (ii) the expression of the kisspeptin mRNA in the brain; and (iii) assessment of immunohistochemistry (IHC) of brain and testis. To further investigate whether testosterone reduction due to SD could affect erectile tissue, an additional 24 rats were divided into

3 groups (control, SD, and SD with T supplementation [SDT]) and compared: (i) T and cortisol levels were quantified, and (ii) endothelial nitric oxide synthase (eNOS)/ neuronal nitric oxide synthase (nNOS)/NOX-2 expression in cavernosal tissue was assessed by measuring mRNA levels and performing Western blotting and IHC. In cavernosal tissues, levels of the eNOS/nNOSmRNAs and proteins tended to be lower, and NOX-2 levels (mRNA and protein) tended to be higher in the SD group than those in the control group and SDT group. IHC for eNOS/nNOS revealed lower-intensity staining in the SD group than in the control and SDT groups, whereas the NOX-2 intensity was higher in the SD group than in the other groups. A lower cortisol level was observed in the control group than in the SD and SDT groups, whereas the level was similar between the SD and SDT groups. The ICP/MAP values were also decreased in the SD group but not on testosterone injection. This study could imply that even short-term SD can produce secondary hypogonadism, impairing men's health. Apart from its potential value in the knowledge of SD consequences to men, it also has a great value as a potential educational tool for a better sleep hygiene.

PREMATURE EJACULATION

Wayman C, Russell R, Tang K, et al. Cligosiban, a Novel Brain Penetrant Selective Oxytocin Receptor Antagonist, Inhibits Ejaculatory Physiology in Rodents. J Sex Med. 2018; 15: 1699–706.

Although in recent years the targeting of neurotransmitters and receptors has changed the treatment of ejaculation disorders, namely premature ejaculation, the ideal drug is far from available. Evidence suggests a major role for serotonin and dopamine in the control of ejaculation reflex, but also other neurotransmitters including oxytocin (OT) are likely to play a role. Epelsiban, an OT receptor antagonist was reported to inhibit ejaculation in rats on central or spinal dosing but showed only limited effects after systemic dosing, consistent with impaired brain penetration. It was studied in a clinical setting and it was reported that it had no clinically or statistically significant change in intravaginal ejaculatory latency time (IELT). The authors speculated that maybe a more centrally penetrant OT receptor

antagonist might have different results. The aim of the current study was to evaluate if cligosiban, a new OT receptor antagonist selectively inhibits human OT receptors, penetrates central nervous system (CNS), shows pharmacology in the CNS, and effects ejaculatory physiology in pre-clinical systems. *In vitro* potency and selectivity of cligosiban was assessed using recombinant and native OT receptor systems including both neuronal and non-neuronal cell types. Selectivity was determined over neighbouring V_{1A} , V_{1B} and V_2 vasopressin receptors. To determine an effect on central OT receptors and on ejaculation, the substance was evaluated in 2 anesthetized rat models – the electromyography model of ejaculatory physiology and a model of OT-mediated CNS neuronal firing. The CNS penetration of cligosiban was also determined by measuring cerebrospinal fluid and plasma drug concentration following intravenous infusion in rats. The *in vitro* and *in vivo* testing showed that cligosiban is a potent selective antagonist at the OT receptor, and it demonstrated CNS penetration and pharmacology by modulating an OT-mediated response in the NTS. It was also shown that cligosiban interrupts the expulsion phase of ejaculation by reducing the normal bulbospongiosum burst pattern and reducing the expulsions that accompany bursts. It seems that it is a promising compound to test the hypothesis that antagonism of central OT receptors might be of therapeutic benefit in the treatment of premature ejaculation. We just hope that it will not have the same disappointing performance in clinical trials as epelsiban.

PEYRONIE'S DISEASE

Ilg MM, Mateus M, Stebbeds WJ, et al. Antifibrotic Synergy between Phosphodiesterase type 5 Inhibitors and Selective Oestrogen Receptor Modulators in Peyronie's Disease Models. Eur Urol. 2019. 75: 329–40

Peyronie's disease (PD) is a fibrotic disorder of the penile tunica albuginea (TA) characterized by the formation of plaques that can lead to deformity and erectile dysfunction. Myofibroblasts seem to be key cells in the pathogenesis of PD and inhibition of myofibroblastic transformation has been suggested as a

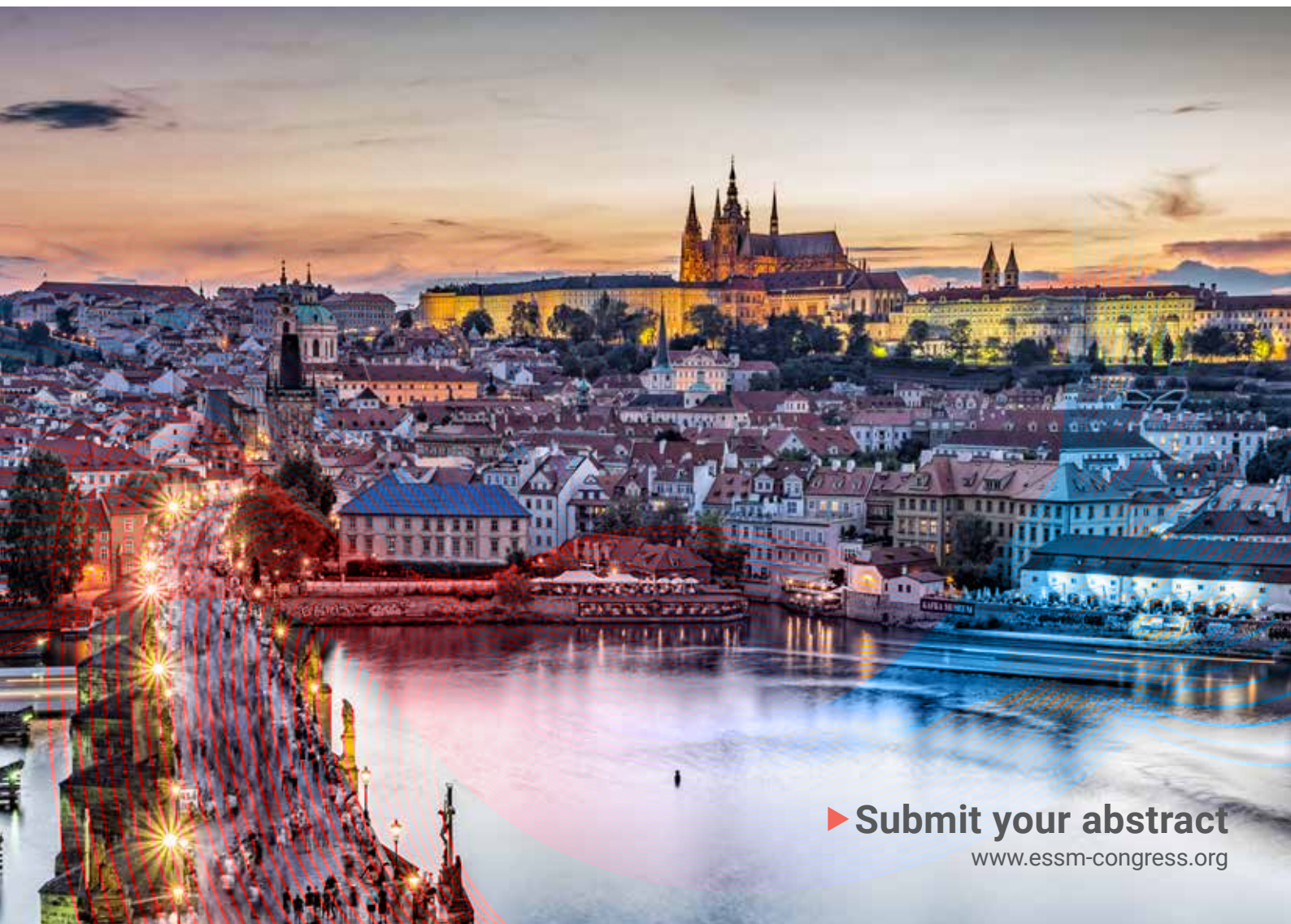
therapeutic option. The authors developed a phenotyping screening assay capable of reproducibly measure transformation of human primary TA-derived fibroblasts to myofibroblasts in a high-throughput format and then tested 21 compounds/drugs that have been suggested to be efficacious in *in vitro*, *in vivo* animal and human studies of PD. They identified 2 classes of drugs that were able to inhibit myofibroblast transformation: phosphodiesterase type 5 (PDE5) inhibitors and selective oestrogen receptor modulators (SERM). When applied together these 2 classes showed synergistic activity both *in vitro* and *in vivo*. These results suggest that this combination might be beneficial in the acute phase of the disease and should be tested in a prospective randomized clinical trial.

Milenkovic U, Ilg MM, Zuccato C, et al. Simvastatin and the Rho-kinase Inhibitor Y-27632 Prevent Myofibroblast Transformation in Peyronie's Disease-Derived Fibroblasts via Inhibition of YAP/TAZ Nuclear Translocation. BJU Int. 2019; 123: 703–15

Currently available treatment options for Peyronie's disease (PD) are merely symptomatic and do not target the underlying pathophysiological processes leading to plaque formation. The search for the molecular mechanisms that lead to the development of PD and ways to interfere with them are the goals of many researchers in this field. The objectives of the current study were to uncover the anti-myofibroblast (MFB) properties of Rho-kinase inhibitor Y-27632 and simvastatin in an *in vitro* and an *in vivo* model of PD. Tissue samples from tunica albuginea (TA) were collected prospectively from 5 patients receiving surgery for PD. Human fibroblasts were isolated from these samples. To induce MFB status, cells were stimulated with TGF- β 1. Increasing doses of Y-27632 and simvastatin were added. RT-qPCR was used to assess mRNA expression of alpha-smooth muscle actin (α -SMA), collagen III, elastin and CTGF after 72 h. WB was used to quantify α -SMA protein contents and IF visualized MFB differentiation by staining for α -SMA after 72 h. Resazurin-based assay was performed to assess cell viability to ensure anti-MFB effect of the drugs. A mechanistic study was performed using IF staining for YAP/TAZ nuclear translocation. Unstimulated, harvested

cells stained positive for vimentin and negative for α -SMA, while desmin mRNA levels were nearly undetectable. Stimulation of the cells with TGF- β 1 caused a significant increase of α -SMA expression on mRNA and protein level, suggesting a myofibroblast phenotype. They also observed an increased level of extracellular matrix (ECM) (collagen I, III and elastin) and CTGF mRNA production, suggesting an upregulation of CTGF in TGF- β 1 stimulated PD-derived fibroblasts. They also found that Y-27632 could significantly impede TGF- β 1 induced myofibroblast transformation, as evidenced on an mRNA and protein level, while there was also a significantly reduced expression of CTGF and collagen III. This data suggest that ROCK-inhibitors can inhibit the formation of myofibroblasts, and hence inhibit their secretory capabilities. The authors suggest

that TGF- β 1 signalling in TA-derived fibroblasts occurs through ROCK-mediated YAP/TAZ nuclear translocation and that this nuclear activity of YAP/TAZ leads to transcription of several pro-fibrotic genes, including collagens and CTGF. Their findings also suggest that active plasma levels of simvastatin could be beneficial for inhibition of fibroblast to myofibroblast transformation and thus impeded fibrogenesis in a clinical setting. They have shown that simvastatin is a very potent inhibitor of myofibroblast transformation, production of ECM (collagen I, III and elastin) and CTGF mRNA. Additionally, the proliferation of PD-derived FBs was attenuated compared to controls or TGF- β 1 stimulated cells. Further investigation of this pathway may eventually lead to novel treatment targets.



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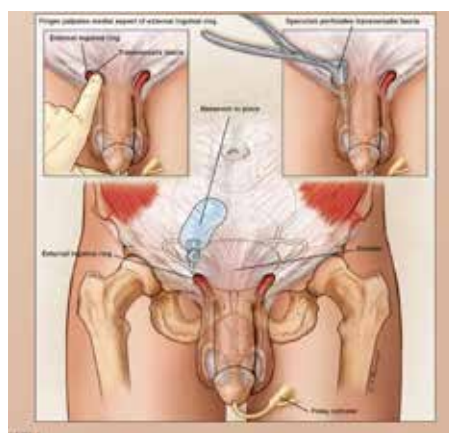
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Reservoir complications in penile inflatable implants

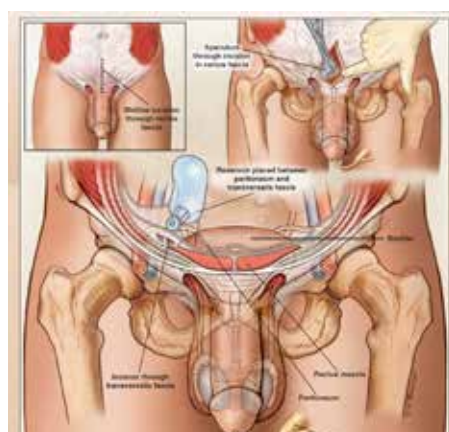
IPP surgery offers a high satisfaction rate and low rate of complications when performed by experienced surgeons. Penile prosthesis reservoir complications are unusual, and mechanical failure or spontaneous rupture of the reservoir is almost unheard of in the modern era. The most serious and feared complication with IPP surgery is infection, with the reported incidence after primary placement 1–3% and after revision surgery 8–18% [3].

The original inflatable penile prosthesis (IPP) reservoir placement is below the transversalis fascia in the space of Retzius.



However, reservoir placement, either in the space of Retzius (SOR), or alternative/ectopic locations, may lead to an array of serious complications that may require revision surgery.

In 2002, Dr. Steve Wilson described ectopic reservoir placement, thereby providing a safe and effective alternative for implant surgeons. This approach tried to stop the need for a second incision and decreased operative times during surgery. Thirteen years after Dr. Wilson's pivotal study, this technique should be in the armamentarium of all urologic prosthetic surgeons.



Accordingly, in certain subsets of patients, ectopic/ high submuscular reservoir site placement should be considered a safe, effective alternative to standard reservoir placement in the space of Retzius. Placement of penile prosthetic reservoirs in the space of Retzius has historically been the standard of care but Ectopic placement of reservoirs could be performed also in all patients with a history of surgical procedures obliterating the space of Retzius (post RP, New bladders, mesh hernioplasty).

Alternative reservoir placement is safe and mechanically reliable approach including in men with prior pelvic surgery. However, there are also associated risk, including reservoir herniation, leakage, tubing torsion, muscle discomfort and unintended reservoir malposition which may require surgical revision [1]

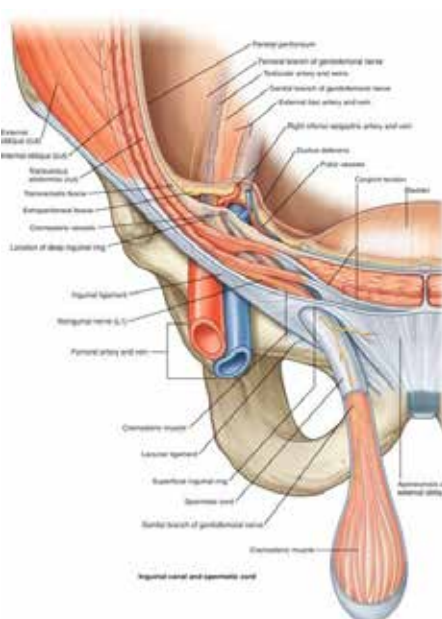
Stember et al demonstrated that ectopic reservoirs had higher complication rates (herniation 1.3% VS 0.1%), revision for palpable reservoir 0.5 VS 0%, Auto-inflation 0.5 VS 0%) [2]



Non-infectious reservoir-related complications in the intraoperative setting include injury to pelvic structures such as bladder, bowel, and blood vessels.



Reservoir erosion into the bladder or bowel is unusual. Vascular injury during or following placement of a reservoir is certainly possible during the digital or sharp dissection to enter the space of Retzius, as the external iliac system is in close proximity. Certain predisposing conditions are believed to increase the risk of reservoir erosion, including prior pelvic surgery or radiation and full bladder during the procedure. In this cases



To reduce the creation of inguinal floor weakness and to reduce the potential risk of visceral injury particularly after prior pelvic surgery, current practice is to enter the space of Retzius sharply. This technique typically makes a hole just large enough for the index finger to gain entry and complete the dissection. If the space of Retzius cannot be entered due to extensive scarring, then ectopic placement may

Ectopic high submuscular reservoir placement can be considered as an alternative method of reservoir placement during IPP implantation (Level2, Grade C). In very obese patients, subcutaneous reservoir can be used with caution (level2, Grade C)



In many cases, It is mandatory remember to do not hesitate to make a short second incision when it is needed and play safe, because single incision is better and faster but **"In medio stat virtus"**.

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Dr. Roberto Larocca

Urology Unit University Federico II
of Naples, Italy

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