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ESSM TODAY

European Society for Sexual Medicine

Contents

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Welcome Message

Fusco, F.
Italy

Dear ESSM Members,

Dear friends,

ESSM wishes you all the best, and confirms the most solid commitment to be at your side in any possible way to improve sexual medicine in Europe and in the world. The Covid-19 pandemic is still a big presence in the background but everybody has now become used to coexist with the new rules that this emergency state imposes. ESSM has learned very quickly to lead the way even in such a tough time, with a number of great web-based initiatives. However the dark age of isolation might have come to the end, and we are very close to meet again in presence in the Rotterdam meeting, where ESSM will continue to provide us with the best possible scenario to shake hands and continue side by side our walk toward clinical improvement and scientific upgrade.

It will be great to see you all again in person.

It will be a moment that we are not going to forget.

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OUT OF THE COVID-19 PANDEMIC: ESSM GO BACK TO NORMAL LIFE?

Carlo Bettocchi
ESSM President

Dear ESSM Family,
Dear Friends,

After more than one and half year of living in the COVID-19 pandemic, we can all say that the virus changed life as we know it—and it may have changed us individually as well, from our morning routines to our life goals, priorities, and careers. In these days, if the vaccines drive down infections and variants are kept at bay, life could return to some form of normal; needless to say we all cant' wait for it! ESSM DOES NOT WANT TO GO BACK TO NORMAL LIFE, WE LOOK FOR THE EXTRAORDINARY!

The ESSM has strongly reacted to the pandemic and despite all the restrictions, we have achieved a number of successful goals that went far beyond our expectations:

WEBINARS (free for everyone and available on the Society website)

- Position Statements webinars in 2020 with 1.175 attendees
- 4 workshop webinars in 2020 and January 2021, with 515 attendees
- 3 webinars supported by IBSA (1 held in April and 2 scheduled in September and October)

VIRTUAL EVENT: our congress 2021 in Rotterdam has been postponed to 2022, but we were able to set up a virtual event (available on the Society website) that, let me stress this once more, was a great success:

- 1.800 Attendees from 107 Countries
- 10 Scientific Sessions with 78 Faculty Members
- 7 Industry Session and 1 supported talk by the industry

We launched the ESCAP (ESSM Scientific Collaboration and Partnership) project, aiming to connect the well-known sexual medicine experts from different sexual societies with young talented authors in order to create a fruitful group aiming to publish reviews or metanalysis in the top journals in the field of sexual medicine.

We are working on new projects, and we will soon be launching the ESSM Surgical Academy that we expect to be the must-attended educational program for surgeons in the field of sexual medicine. The educational path will include live webinars, textbooks and an exclusive video library, to end with a fellowship at centers of excellence. We look forward to our members involvement!

Last, but most important, we are planning on coming back to a face-to-face congress in February 2022 in Rotterdam, where we are willing to offer the most interesting scientific program and welcome all those that are missing live events! Stay tuned, we can't wait to see you in The Netherlands; ESSM does not expect to go back to normal life, our motto for 2022 is **ESSM DOES IT BETTER!**

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Chronic Testicular Pain: an overview

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Chronic testicular pain (CTP) is defined as an intermittent or constant, unilateral or bilateral pain of three or more months duration that is significantly bothersome to the patient and other causes such as an infection, testicular mass, varicocele, hydrocele, abscess or referred pain have been ruled out (1,2). It may occur accompanied by pain with sexual intercourse, physical activities and/or ejaculation (3)

CTP is the cause of about 2.5% to 5% of all urology consultations (4). One of the most common causes of this pathology is the history of previous vasectomy surgery and this entity is known as "post-vasectomy pain syndrome, PVPS" (5). The approximate incidence of PVPS is estimated at around 1-15 out of every 100 vasectomized (6–8). Other recognized causes of CTP are inguinal hernia surgery (9), abdominal surgery (10)n=40, diabetic neuropathy (11) and imipramine used as an antidepression treatment (7). In patients with hyperuricemia, intracanalicular deposition of uric acid crystals with consequent disruption of the nerve endings has been suggested as the cause of this condition (12). Some patients relate the onset of their chronic testicular pain to some kind of injury. This could be explained by the phenomenon of neural plasticity. In neural plasticity, injury can cause changes at all levels of the nervous system, so pain messages are amplified.

Chronic testicular pain can be considered as part of chronic pelvic pain syndrome and the etiology and pathophysiological mechanism is not fully understood. The importance of the sympathetic nervous system and the role of a possible alteration of the adrenergic receptors of the vas deferens are discussed (7). In PVPS, a mechanical obstruction of the ejaculating ducts with congestion of the epididymis, a nervous entrapment, formation of granulomas or formation of perineural fibrous tissue are postulated as possible causes (13). Other authors affirm that the pain may be caused by the disruption of the neurovascular bundle, in particular, those that move along the vas deferens and contain sympathetic nerves derived from the pelvic plexus and the afferent nociceptive nerves. The alteration of these nerves can lead to dyssynergia of the vassal contractions or to scarring with the consequent neural compression that gives rise to pain. (14)

For a proper diagnostic approach, a good anamnesis is necessary, recording the date the pain onset, concomitant diseases, previous surgeries and possible triggers, as well as the type of pain, location, intensity, irradiation and triggering or other aggravating factors.

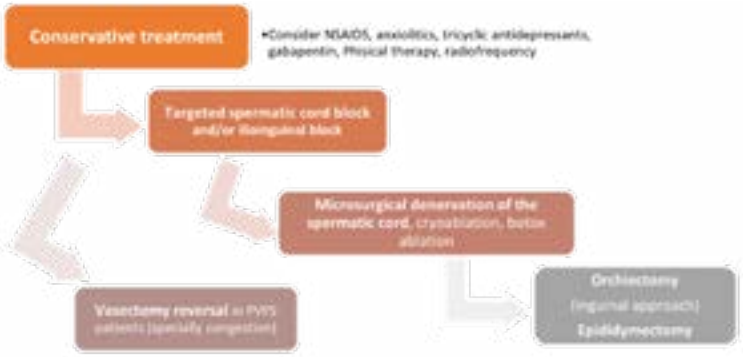
Although there are potential causes of CTP, such as epididymis congestion, infection or varicocele, most of these can be ruled out with a complete medical history, physical examination and urinalysis. When these analysis are normal, the diagnosis is less clear and the neurogenic causes of pain must be considered (15). If there is no suspicion of infection, treatment with empirical antibiotic therapy is not indicated (16).

Scrotal ultrasonography is usuallypart of the patient's evaluation with scrotal pain. However, in the absence of significant clinical findings on physical examination and in the presence of a negative urinalysis, the real benefit of scrotal ultrasound is to reassure the patient concerned about cancer (17).

Currently, the treatment of CTP is largely empirical because of the absence of standardized protocols (2) and it occupies a considerable part of most urologists' time. Chronic testicular pain typically presents a poor response to usual analgesic drugs and as a first line of treatment, low doses of anxiolytics or tricyclic antidepressants (amitriptyline, dapoxetine and nortriptyline) can be used with good rates of pain reduction (18). Neuromodulating drugs such as gabapentin that provide significant pain reduction in up to 80% of patients may also be used (19) (***Figure 1)***.

FIGURE 1: CHRONIC TESTICULAR PAIN MANAGEMENT PROPOSED ALGORITHM

NSAIDS: non-steroidal anti-inflammatory drugs



Other conservative strategies include pelvic floor physical therapy, acupuncture, transcutaneous electrical nerve stimulation (TENS) (20,21)which may be either unilateral or bilateral, lasting for more than 3 months. It disturbs a patient's daily activities and quality of life (QoL, or neuromodulation (2). Cohen ***et al.*** (22) standardized treatment exists. We report 3 patients with groin pain or orchialgia who were treated with pulsed radiofrequency of the nerves innervating these areas. All 3 patients reported complete pain relief at their 6-month follow-up visits. The techniques and settings used for the nerve blocks and radiofrequency procedures are explained in detail, along with a brief synopsis of the rationale for using it. Randomized, placebo-controlled studies are needed to better assess the efficacy of this procedure and identify eligible candidates.","container-title":"Urology","DOI":"10.1016/s0090-4295(02 and Misra ***et al***. (23) reported their results using pulsed radiofrequency of the scrotal nerves that appears to be a safe minimally invasive outpatient procedure and recommended further randomized, placebo-controlled studies to assess the procedure efficacy.

A specific block of the spermatic cord and/or ilioinguinal nerve with local anesthesia with or without steroids has also been suggested, as an intermediate maneuver between conservative and surgical treatment, in order to alter the route of afferent pain (5). This can be used as a diagnostic procedure, as it confirms a neural source of pain (16,24). The effects of these blocks are usually short-lived, and the pain usually returns. However, these blocks provide a significant predictive value in response to surgical treatments. A positive response is considered an independent predictor of response to microsurgical denervation of the spermatic cord.

The ilioinguinal nerve comes from the first lumbar branch and the 12th thoracic branch and is responsible for the innervation of the cremaster muscle and the sensitivity of the scrotal content and the base of the scrotum skin ***(Figure 2)***. A group of sympathetic fibres follow the path of the spermatic cord and collect the scrotal content sensitivity. The ilioscrotal nerve enters the scrotum through the anterolateral border of the spermatic cord and it is accessible to the pharmacological anaesthetic block. When performing an ilioscrotal nerve block, there is no anaesthesia of the scrotal skin (26, 27).

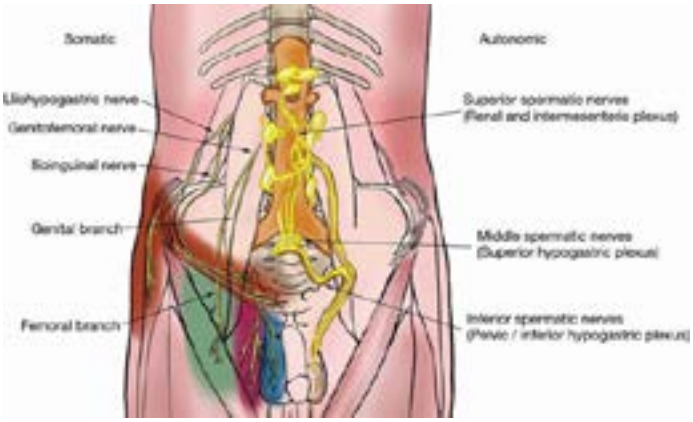


FIGURE 2: SOMATIC AND AUTONOMIC NERVES SUPPLYING THE SCROTAL CONTENTS.

Source http://tau.amegroups.com/article/view/14984/15154. © 2017 by Dhairya Patel, based on Reynolds LW, Sills SM. Orchialgia. In: Waldman SD. editor. Pain Management, Philadelphia: Elsevier, 2011.

The spermatic cord block is performed starting with palpation of the pubic tubercle and inserting the 22-gauge needle one centimetre from the tubercle and following the caudal and vertical direction towards the anterior face of the pubic bone. On its way, contacts the bone after it has passed through the spermatic cord. The liquid is injected along the withdrawal route to the skin after aspiration to avoid intravascular injection of local anesthesia ***(Figure 3)***.

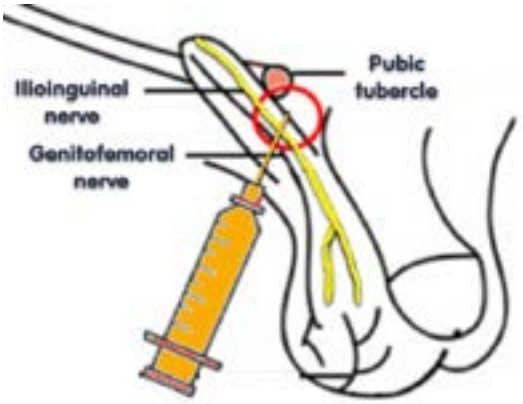


FIGURE 3: SPERMATIC CORD BLOCK

Tan ***et al.*** use blockades with bupivacaine 0.75% when there is a failure of medical treatment, offering a series of 4-5 cycles repeated every 2 weeks if a symptomatic relief is produced. Surgical therapy is recommended when conservative treatment fails (28).

For patients with CTP who do not respond to conservative treatment, different surgical procedures have been described (29) as there is no clearly established effective treatment regimen, nor is there a recognized and accepted standard protocol for evaluation. Many of these patients will see multiple physicians during the course of their evaluation, further increasing their frustration and potentially straining the physician/patient relationship. The etiology of testicular pain is varied and is frequently idiopathic. Easily recognized and reversible causes include spermatocele, tumor, infection, varicocele, and torsion. Chronic orchialgia has been defined as at least 3 months of chronic or intermittent pain.

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Although the diagnosis of chronic orchialgia is frequently given to these patients, it should be recognized that fairly frequently the patient will not have just testicular pain, but may have pain involving the epididymis, vas deferens, or adjacent paratesticular structures. Therefore a more appropriate term would be chronic scrotal content pain. This article reviews the current understanding of chronic scrotal content pain, reviewing the etiology, evaluation, and then a systematic review of the published literature on treatment. It should be recognized that the majority of the published literature are cohort studies with limited numbers of patients, rarely placebo-controlled, and without a uniform standard evaluation. Microdenervation of the spermatic cord is emerging as a reasonable and effective outpatient surgical technique to resolve chronic scrotal content pain, and successful results appear to be predicted by a temporary but complete response to a spermatic cord block.Epididymectomy has a very variable success rate from 10% to 80% (6, 30), and it is recommended when there is refractory pain to conservative maneuvers, localized at that level, especially in those with structural abnormalities such as cysts observed on examination or ultrasound.

Recanalization by vasovasostomy or epididimovasostomy has also been described for the treatment of PVPS, also with variable results and improvement rates around 60-80% of cases (3, 15, 31, 32)tender sperm granuloma and/or nerve entrapment at the vasectomy site. To our knowledge nerve proliferation has not been evaluated previously as a cause of pain. Vasectomy reversal is reportedly successful for relieving pain in some patients. We report our experience and correlate histological findings in resected vasal segments with outcome to explain the mechanism of pain in these patients.\nMATERIALS AND METHODS: We retrospectively reviewed the records of 13 men who underwent vasectomy reversal for the post-vasectomy pain syndrome. We compared blinded histological evaluations of the vasal ends excised at vasectomy reversal in these patients with those of pain-free controls who underwent vasectomy reversal to reestablish fertility. Controls were matched to patients for the interval since vasectomy. Histological features were graded according to the degree of severity of vasitis nodosum, chronic inflammation and nerve proliferation.\nRESULTS: Mean time to pain onset after vasectomy was 2 years. Presenting symptoms included testicular pain in 9 cases, epididymal pain in 2, pain at ejaculation in 4 and pain during intercourse in 8. Physical examination demonstrated tender epididymides in 6 men, full epididymides in 6, a tender vasectomy site in 4 and a palpable nodule in 4. No patient had testicular tenderness on palpation. Unilateral and bilateral vasovasostomy was performed in 3 and 10 of the 13 patients, respectively. Postoperatively 9 of the 13 men (69%. As for the resection of granulomas, these appear with a very disparate frequency between 5-70% and occurs as a natural effect and not as a complication in vasectomy techniques. In case it produces chronic pain located at the site of the granuloma refractory to the previous measures or if the skin fistulizes (an uncommon fact) its resection is justified (28).

Finally, microdenervation of the spermatic cord (MDSC) is a well-studied option and remains a valuable approach with high success rates and should be considered for CTP that is refractory to medical therapy. This treatment appears to show the highest success rate for patients who experience temporary relief from a spermatic cord block, and can significantly improve patients' quality of life and ability to return to daily activities (16, 28). ***Figure 4.***

New minimally invasive procedures such as laparoscopic or robotic testicular denervation, have been emerging to support in the management of chronic refractory pain with a significant reduction in pain presenting low morbidity and mortality (6, 28, 33).

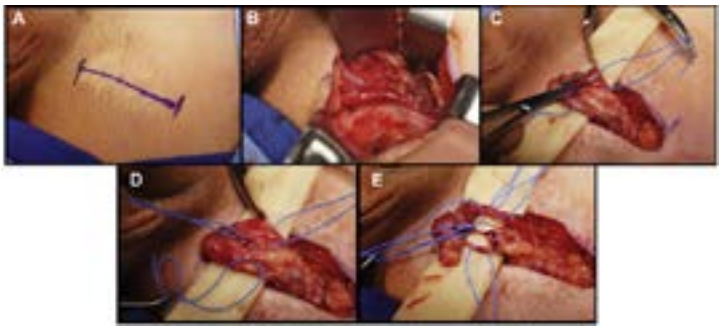

FIGURE 4: MICRO-DENERVATION OF THE SPERMATIC CORD.

A: marking of the inguinal site. B: dissection to expose the spermatic cord. C: spermatic cord with the cord fascia opened. D arteries secured by a blue vessel loop. E: after completion of dissection, only the cremasteric artery, testicular artery, deferential artery, and lymphatics remain (top to bottom). Source: Tan, W. P., & Levine, L. A. (2018). Micro-Denervation of the Spermatic Cord for Post-Vasectomy Pain Management. Sexual Medicine Reviews, 6(2), 328–334. doi:10.1016/j.sxmr.2017.06.002

In conclusion, chronic testicular pain is a debilitating and difficult to treat condition and remains a challenge for urologists. A thorough understanding of this pathology and its different causes, and a multidisciplinary team approach to its treatment, are necessary for the patient to benefit from the different available options.

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Penile re-modeling in Peyronie's disease: Bend the Curve

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Peyronie's disease (PD) can cause significant physical and psychological impact on the quality of life by causing erectile dysfunction and penile curvature. The exact etiology of PD is still unknown, but most agree that repetitive microtrauma to penile tunica albuginea leads to this collagen disorder. Penile curvature could be ventral, dorsal, lateral, combined, or hourglass deformity. The management of penile curvature alone in the absence of erectile dysfunction in PD gets tricky.

A substantial number of men (21-46%) notice significant reduction in erectile function after plaque incision/excision and grafting without a penile prosthesis in PD [1-2]. Hence one should explore all possible remodeling options to correct penile curvature without incising/excising the plaque. Traditionally most interventions to correct penile curvature were limited to the chronic phase of PD, but there has been a recent shift in targeting the disease as early as in the acute phase [3-4]. Penile re-modeling (without incising /excising the penile plaque) can be done with or without assisted devices during different stages of management of PD.

Various penile re-modeling strategies include vacuum device (VD), penile traction device (PTD), intralesional Collagenase Clostridium histolyticum (CCH) injection, manual modeling over a penile prosthesis intra-operatively, modeling at home over a penile prosthesis and combined modeling (combination).

For the ease of understanding, the modeling procedures can be sub-grouped into three sections: non-surgical, intra-operative and post-operative.

1. NON-SURGICAL:

a. Collagenase Clostridium histolyticum (CCH) injection & modeling,
b. Vacuum device (VD)
c. Penile traction device (PTD)

CCH & Modeling:
The IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II examined the clinical efficacy and safety of CCH intralesional injections in subjects with PD [5]. IMPRESS regimen consisted of 4 cycles. One cycle involved 2 CCH injections given 1-3 days apart, followed by modeling first done by healthcare worker and subsequently by the patient for 6 weeks at home. Modeling technique involved applying pressure for 30 seconds to stretch the penis in opposite direction of curvature keeping plaque as the fulcrum. A post-hoc meta-analysis of IMPRESS I and II data reported that the CCH group noted 34% improvement (mean -17.0±14.8° change per subject) in mean penile curvature compared with a mean 18.2% improvement in placebo-treated subjects. Three cases of corporal rupture (serous adverse event) were repaired subsequently.

There have been no published results of CCH in PD from Asian countries probably due to higher cost, lack of insurance coverage or more importantly non-availability of CCH in Asian countries. European urologists were in for a surprise shock about discontinuation of CCH in Europe in November 2019 [6]. Currently the CCH is restricted to USA alone.

Vacuum device (VD):
Animal studies have shown antiapoptotic, antifibrotic, and smooth muscle preserving effects of VD [7]. The role of VD in PD is still evolving and at present the use of vacuum device has shown 5–25 degree improvement in curvature [8]. More studies are required to substantiate the role of VD in PD.

Penile Traction Device (PTD):
PTD helps in modeling by mechanotransduction, a concept that has been borrowed from orthopaedics. The use of mechanical traction and tissue expansion therapy results in changes in connective tissue by cellular proliferation and expansion of the extracellular matrix.
PTD can be used as a monotherapy or as a combination therapy. There are various models of PTD which include Andropenis®, Andropeyronie®, FastSize Medical Extender®, Penimaster Pro® system and RestoreX®. Monotherapy with PTD has shown improvements in curvature ranging from 14-32 degrees in both acute and chronic phase of PD.
PTD combination therapy has been done either with oral therapy, intralesional therapy or surgical therapy. A significant limiting factor of PTD is the duration of application of these devices which is usually around 4-6 hours/ day except the latest RestoreX® which is applied for 60-90 minutes/day [9].

2. OPERATIVE:

The term "manual modeling" was first described by Wilson & Delk in 1994 [10]. It was an intraoperative manoeuvre after placement of penile prosthesis to correct residual curvature in PD with a reported success rate of 86 % (118/138). Although this technique met with a storm of criticism when it was first published, it subsequently became a standard treatment protocol in most centres worldwide.

Wilson's intra-operative manual modelling involved bending the penis in opposite direction of curvature for 90 seconds over the penile prosthesis after securing the corporotomy site and the pump tubing. Second (final) attempt may be attempted if residual curvature persists. The concern of higher device malfunction after manual modeling is still debatable.

3. POST-OPERATIVE:

The usual dictum is that residual curvature of more than 30 degree even after manual modeling over PP warrants placement of a graft. Moncada et al published a structured home-modeling (HM) protocol in residual curvatures of up to 45 degrees to avoid additional grafting surgeries [11]. At 3 and 6 months, 85.5% and 94.7% of the patients had < 10-degree residual curvature respectively. Moncada's HM protocol was first instructed in clinic by the urologist after 4 weeks of surgery and subsequently done by the patient himself at home. Each cycle of the protocol involved bending the penis for 30 sec in opposite direction of residual curvature after full inflation of inflatable PP and many such cycles were done in a day for a total of 6 months.

Rybak et al noted that post-operative combination therapy with PTD for 2–6 hours daily starting 3–4 weeks post-operatively had significantly greater mean increase in stretched penile length when compared to without PTD (1.48 cm vs 0.24 cm) [12].

CONCLUSION:

One should explore the various re-modeling options to straighten the penis in PD before attempting to incise/excise the plaque thereby preserving the native erectile and penile sensory functions of PD patients. The penile traction device is being increasingly studied since last decade and is evolving as a feasible non-operative modality with less complications. Manual modeling continues to be practised intra-operatively over penile prosthesis to correct residual curvatures. More studies are required to validate the role of vacuum device in PD. The future of collagenase injection is uncertain considering its higher costs and non-availability in most continents.

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Benign prostatic hyperplasia surgery and Sexual Function: What is the evidence?

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a highly prevalent disease in men over 50 years old, and its incidence increases with age. Prevalence of BPH is estimated as 50% of men in their 50s, and reaches 80% for men over 80 years [1]. Patients with BPH often present with varying severity of lower urinary tract symptoms (LUTS), although these can occur in the absence of BPH and vice versa [2]. The primary aim of therapy of BPH is to reduce LUTS, which ultimately improves quality of life (QoL) [3]. Despite the advancements in pharmacological treatment of BPH during the last decades, surgery currently remains a fundamental option in the management of the patient. Surgical treatment of BPH is indicated in patients who are refractory or intolerant to medical therapy and in patients with complications resulting from the disease [4]. It is widely accepted that surgical procedures for BPH may determine sexual dysfunctions (SD). Numerous sexual side effects, including erectile ejaculatory and orgasmic dysfunctions, were reported with the majority of surgical treatments for BPH [5,6]. Nevertheless, some studies showed no change or even a possible improvement in the sexual function of patients with BPH undergoing surgical therapy [7].

PATHOPHYSIOLOGY

The worsening of sexual function can result from several mechanisms following BPH surgery [8-13].

- Injury of the internal urinary sphincter. Ejaculatory dysfunction represents the most commonly reported side effect of many treatments for BPH. In the normal genitourinary tract, the involuntary smooth muscle of the internal urethral sphincter plays a critical role in maintaining antegrade ejaculatory function. Disruption of this mechanism is the predominant factor underlying BPH surgery-related retrograde ejaculation (RE). Psychological repercussions of RE can affect sexual satisfaction and contribute to erectile dysfunction (ED).
- Psychological impact of recent surgery on sexual desire and on sex-related distress.
- Direct injury of neurovascular bundles following capsular perforation. This is a rare adverse event (AE).
- Indirect thermal injury to neurovascular bundles. It is a controversial pathophysiological mechanism.
- Urinary catheter. It mechanically prevents sexual intercourse in the first days after BPH surgery.

The improvement of sexual function can arise from two main factors following BPH surgery [14-18].

- Discontinuation of medical therapy for BPH. Drugs for BPH, taken by patients before surgery and suspended after the procedure, have a negative impact on sexual function. Alpha-blockers are associated with RE or anejaculation, while 5-alpha reductase inhibitors can cause decreased libido and ED. It is important to emphasize that discontinuing medical treatment for BPH can be a confounding factor in clinical trials evaluating sexual function, however, it is difficult to limit this bias due to ethical reasons.
- Improvement of LUTS. SD and LUTS are both highly prevalent and frequently co-associated in the same aging male group. In recent years, the investigators have hypothesized a common pathophysiology to explain this correlation regardless of shared risk factors, although a specific causal relationship has not yet been defined. It is essential to emphasize that since SD often pre-exist BPH surgery, patients should be adequately evaluated prior to surgical procedure to avoid mistakenly considering them as postoperative complications.

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While surgical factors (surgical technique, characteristics of energy, experience of the surgeon) must be considered, patient factors should also be taken into account. Patient characteristics could predict which subjects are more likely to have modifications of the sexual function following BPH surgery. Patients with normal erectile function are at more risk of having a reduction in erectile function following surgical treatment; on the contrary, the worse the erectile function is before surgery, the more the patient has to gain in erectile function due to treatment. Similarly, the greater the severity of the LUTS, the greater the improvement that can be achieved by surgical treatment and consequently the positive impact on sexual function [7].

THE EVIDENCE

Most studies focus on surgical and functional outcomes of BPH surgery, while sexual outcomes are often uninvestigated or under-investigated. Male sexual function is a complex interplay of psychological, neurogenic, vascular, and hormonal factors. Although it consists of different domains (sexual desire, erectile function, orgasmic function, ejaculatory function, sexual satisfaction), in most cases only erectile and ejaculatory functions are evaluated, being ED and RE the most frequently reported sex-related complications. The use of non-validated and arbitrary tools is extremely common for the assessment of sexual outcomes. The International Index of Erectile Function (IIEF) and its abbreviated forms (IIEF-5, IIEF-EF) are the most widely used validated questionnaires for the evaluation of erectile function, while Male Sexual Health Questionnaire (MSHQ) and its short form (MSHQ-EjD-SF) are the most commonly used tools for the assessment of ejaculatory function. Orgasmic function, sexual satisfaction, and sexual desire are very rarely investigated and the use of validated instruments to measure these outcomes is unusual. Finally, most of the studies on BPH surgery including the assessment of sexual outcomes are case series with no control group, this methodological issue limits the strength of the resulting evidence [4,19,20].

Transurethral resection of the prostate (TURP) remains the gold standard surgical treatment for BPH in patients with small prostates (30-80 mL), being the reference procedure in most comparative studies [4]. TURP is associated with a high prevalence of RE (70-90%), however, it does not seem to have a negative impact on erectile function. No difference in sexual AEs between monopolar and bipolar TURP are clearly demonstrated [21-24]. Laser surgery for BPH is currently part of common clinical practice, with laser enucleation becoming the treatment of choice for patients with large prostates (>80 mL) [4]. Overall, no significant differences were found in the RE rate compared with TURP. No negative effect was demonstrated on erectile function, similarly to TURP [25,26]. Several ejaculation preservation techniques were developed to preserve the ejaculatory function (e.g., ep-TURP, ep-HoLEP, etc.). They seem reasonable options for this purpose but only limited and heterogeneous evidence is available [27].

In the recent years, there was an increased interest in the development of minimally invasive treatments for BPH, such as Prostatic Urethral Lift (PUL, UroLift®), Water Vapor Thermal Therapy (WVTT, Rezūm™), Waterjet Prostate Ablation (WPA, AquaBeam®), and Temporarily Implanted Nitinol Device (iTIND) to achieve symptomatic improvement similar to traditional surgery, while maintaining sexual function [19]. PUL demonstrated an impact similar to sham therapy and significantly less than TURP on ejaculatory function, besides, it showed an effect not significantly different from sham therapy and TURP on erectile function [28,29]. According to European Association of Urology Guidelines, PUL should be offered in man interested in preserving ejaculatory function [4]. Literature reported an impact of WVTT on erectile and ejaculatory functions comparable to sham therapy [30]. WPA was associated with significantly better ejaculatory function and similar erectile function in comparative studies with TURP [31]. Very limited evidence is available for iTIND, however, sexual function was found stable through years, with no reports of SD [32].

CONCLUSIONS

Sexual activity remains an essential component of overall quality of life in most men regardless of age, therefore, the benefit of reducing LUTS with surgery should be weighed with the risk of causing SD. While more extensive data on sexual outcomes are available for traditional BPH surgery, such as TURP, there is only limited evidence for other surgical procedures. Minimally invasive treatments seem to minimize SD and could be discussed as an alternative, especially in patients who wish to preserve their sexual function. Further studies investigating the impact of BPH surgery on sexual function are needed to improve knowledge of scientific community on the topic and ultimately allow better patient counseling at the moment of therapeutic choice.

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Have you read? Best of the best: basic research

Lourenco, M.

ERECTILE DYSFUNCTION

The Combination of High-Fat Diet and Oral Marijuana Promotes the Development of Fibrosis in the Mouse Corpora Cavernosa.

Nguyen S, Mangubat M, Eleswarapu S, Wilson JB, Molina J, Abraham A, Artaza JN, Friedman TC, Ferrini MG. Sex Med. 2021 Apr;9(2):100312. doi: 10.1016/j.esxm.2020.100312. Epub 2021 Feb 1. PMID: 33540365; PMCID: PMC8072182.

The authors aimed to determine the effects of diet and oral cannabis extract on fibrosis and oxidative stress within the corpora cavernosa of mice. This was a pilot animal study in which groups of 2-month old C57BL/6J male mice were fed a normal chow diet (NCD) or high-fat diet (HFD) daily and treated with or without either marijuana (MJ) or Δ-9-tetrahydrocannabinol extract (THC) extract for 2 months. The combination of HFD with MJ resulted in: (i) a decrease in the smooth/collagen ratio in the corpora cavernosa, (ii) an increase in alpha-smooth muscle actin expression in the tunica albuginea compatible with myofibroblast proliferation, and (iii) a decrease in heme oxygenase 1 expression indicating an increase in oxidative stress. In conclusion, HFD combined with oral MJ extract led to structural alterations in erectile tissue that are associated with accelerated corporal fibrosis.

miR-195-5p Regulates the Phenotype Switch of CCSM Cells by Targeting Smad7.

Zhang J, Zhang X, Cong S, Zhang J, Zhang A, Pan L, Ma J. Sex Med. 2021 Jun;9(3):100349. doi: 10.1016/j.esxm.2021.100349. Epub 2021 Jun 1. PMID: 34087534; PMCID: PMC8240331.

This study aimed to investigate the role of miR-195-5p in regulating the phenotype switch of the corpus cavernosum smooth muscle (CCSM) cells. A small mother against decapentaplegic 7(Smad7) virus vector and a miR-195-5p mimics or an si-Smad7 viral vector and a miR-195-5p inhibitor were transfected into CCSM cells. Overexpressed miR-195-5p promoted the transformation of CCSM cells from a contractile type to a synthetic type. Meanwhile, the migration ability and proliferation ability of CCSM cells increased, and the apoptosis rate decreased. The expression-silencing of miR-195-5p gave rise to the opposite effect. The results of the rescue experiment demonstrated that overexpressed Smad7 rescued the inhibitory of the switch of the CCSM cell phenotype from the contractile type to the synthesis type caused by overexpression of miR-195-5p alone.

Intracavernous Injection of Autologous Platelet-Rich Plasma Ameliorates Hyperlipidemia-Associated Erectile Dysfunction in a Rat Model.

Huang YC, Wu CT, Chen MF, Kuo YH, Li JM, Shi CS. Sex Med. 2021 Apr;9(2):100317. doi: 10.1016/j.esxm.2020.100317. Epub 2021 Jan 30. PMID: 33529811; PMCID: PMC8072173.

The authors investigated latelet-rich plasma (PRP) in a rat model of hyperlipidemia-associated erectile dysfunction (ED). Thirty 2-month-old male Sprague-Dawley rats were randomly divided into 3 groups. 20 rats were fed a high-fat diet for 5 months and were randomly divided into 2 groups: (i) rats in the H group received supernatant injection into the corpus cavernosum weekly for 4 weeks; (ii) rats in the H + PRP group received PRP injection into the corpus cavernosum weekly for 4 weeks. 10 rats were fed a standard diet for 5 months and received supernatant injection into the corpus cavernosum weekly for 4 weeks (N group). 7 days after the 4th injection, all rats underwent erectile function testing. Erectile function was evaluated by measuring intracavernous pressure (ICP) and mean arterial pressure (MAP). Intracavernous pressure/MAP and area under the curve/MAP ratios were significantly higher in the N and H + PRP groups than in the H group. Insulin-like growth factor-1, brain-derived neurotrophic factor, and vascular endothelial growth factor levels were significantly higher in the H + PRP group than in the N and H groups.

Effects of androgen on extracellular vesicles from endothelial cells in rat penile corpus cavernosum.

Yan LT, Yang ZH, Lin H, Jiang J, Jiang R. Andrology. 2021 May;9(3):1010-1017. doi: 10.1111/andr.12980. Epub 2021 Feb 9. PMID: 33484224.

It was reported that eNOS was expressed in androgen may regulate erectile function by affect the release of extracellular vesicles (EVs) from endothelial cells. The authors aimed to investigate whether androgen affects the production of EVs and nitric oxide (NO) in endothelial cells of rat penile corpus cavernosum. Endothelial cells were treated with different concentrations of dihydrotestosterone (DHT) in a cell culture medium as follows: no-androgen group (NA group, DHT 0 nmol/L), very-low androgen group (VLA group, DHT 0.1 nmol/L), low androgen group (LA group, DHT 1 nmol/L), and physiological concentrations androgen group (PA group, DHT 10 nmol/L). Positive expression of CD9, CD63, TSG101,

and eNOS was found in isolated EVs. The concentration of EVs was lower in the NA group compared with other groups. The expression of eNOS and the concentration of NO was lower in the NA group than that in other groups. The authors concluded that the decrease in eNOS-expressing EVs is one mechanism of NO reduction in endothelial cells of rat corpus cavernosum caused by low androgen levels.

Low androgen status inhibits erectile function by increasing pyroptosis in rat corpus cavernosum.

Chen ZB, Li G, Lin H, Jiang J, Jiang R. Andrology. 2021 Jul;9(4):1264-1274. doi: 10.1111/andr.12995. Epub 2021 Mar 11. PMID: 33657666.

The authors aimed to investigate whether low androgen status inhibits erectile function of rats by inducing pyroptosis in the corpus cavernosum (CC). Thirty-six eight-weeks-old healthy male Sprague-Dawley rats were divided into six groups: sham-operated group (4w sham, 8w sham), castration group (4w cast, 8w cast), and castration + testosterone (T) group (4w cast + T, 8w cast + T). The rats in castration + T groups were injected with testosterone propionate subcutaneously. After 4 and 8 weeks, the ratio of maximum intracavernous pressure (ICPmax)/mean arterial pressure (MAP), the level of serum T, the concentration of nitric oxide (NO) and interleukin-1β (IL-1β), the expression of NOD-like receptor pyrin domain containing 3 (NLRP3), apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC), Caspase-1 p20, gasdermin D-N (GSDMD-N), transforming growth factor β1 (TGF-β1), collagen-I, and collagen-III, the ratio of smooth muscle/collagen (SM/C), and the proportion of pyroptotic cells in the CC were analyzed. The ratio of ICPmax/MAP (3/5 V) and SM/C, the level of NO and serum T was significantly decreased in castration groups when compared to other groups. NLRP3, ASC, Caspase-1, and GSDMD were mainly expressed in the cytoplasm of smooth muscle cells (SMCs) and endothelial cells (ECs) in the CC. The expression of NLRP3, ASC, Caspase-1p20, GSDMD-N, IL-1β, TGF-β1, collagen-I, and collagen-III was significantly increased in castration groups when compared with other groups. The proportion of pyroptotic cells in the CC was increased significantly in castration groups when compared with other groups. The authors concluded that low androgen status inhibits erectile function of rats by promoting CC fibrosis and reducing NO synthesis through pyroptosis of SMCs and ECs in the CC.

Increased Level of Tumor Necrosis Factor-Alpha (TNF-α) Leads to Downregulation of Nitrergic Neurons Following Bilateral Cavernous Nerve Injury and Modulates Penile Smooth Tone.

Matsui H, Sopko NA, Campbell JD, Liu X, Reinhardt A, Weyne E, Castiglione F, Albersen M, Hannan JL, Bivalacqua TJ. J Sex Med. 2021 Jul;18(7):1181-1190. doi: 10.1016/j.jsxm.2021.05.001. PMID: 34274042.

The aim of this study was to examine temporal changes of TNF-α, after bilateral cavernous nerve (CN) injury (BCNI), to evaluate effect of exogenous TNF-α on neurite outgrowth from major pelvic ganglion (MPG), and to investigate effect of TNF-α signal inhibition to evaluate effects of TNF-α on penile tone with TNF-α receptor knockout mice (TNFRKO). Seventy Sprague-Dawley rats were randomized to undergo BCNI or sham surgery. Sham rats' MPGs were harvested after 48 hours, whereas BCNI groups' MPGs were at 6, 12, 24, 48 hours, 7, or 14 days after surgery. qPCR was used to evaluate gene expression of markers for neuroinflammation in MPGs. BCNI increased gene and protein expression of TNF-α in MPGs. Exogenous TNF-α inhibited MPG neurite outgrowth. MPGs cultured with TNF-α had decreased gene expression of nNOS. MPGs cultured with TNF-α had shorter nNOS+ neurites than TH+ neurites. Gene expression of nNOS was enhanced in TNFRKO mice compared to WT mice. WT mice showed enhanced smooth muscle contraction of penises of WT mice was enhanced to EFS, compared to TNFKO. Penile smooth-muscle relaxation to EFS was greater in TNFKO mice compared to WT. The authors concluded that TNF-α inhibition may prevent ED after prostatectomy.

Apelin-13 Protects Corpus Cavernosum Against Fibrosis Induced by High-Fat Diet in an MMP-Dependent Mechanism.

Sturny M, Anguenot L, Costa-Fraga FP, Bragina ME, Lima AM, da Silva RF, Fraga-Silva RA, Stergiopulos N. J Sex Med. 2021 May;18(5):875-888. doi: 10.1016/j.jsxm.2021.02.004. Epub 2021 Apr 15. PMID: 33863684.

The authors aimed to investigate the effect of chronic Apelin treatment on the corpus cavernosum structure of hypercholesterolemic mice. Apolipoprotein gene-deleted (ApoE-/-) mice were fed with a Western diet for 11 weeks and received Apelin-13 or vehicle during the last 3 weeks. Penile samples were obtained for histological and biochemical analyses to assess the intracorporal collagen content and key proteins expression. Furthermore, the effect of Apelin-13 was evaluated in cultured NIH3T3 mouse fibroblasts stimulated with TGF-β. Interestingly, 3 weeks of Apelin-13 treatment strongly reduced intracavernosal collagen content. In addition, Apelin-13 enhanced total matrix metalloproteinase (MMP) activity in the mice penis, which was associated with an increased protein expression of MMP-1, MMP-3, MMP-8, and MMP-9, while tissue inhibitor of metalloproteinase were unaltered. These beneficial actions were not associated with changes in nNOS or eNOS protein expression, intracavernosal reactive oxygen species content, or atherosclerotic plaque deposition. These results point out Apelin/APJ system as a potential target to treat intracavernosal fibrosis-related disorders.

Expression of MicroRNAs (miR-15b, miR-16, miR-138, miR-221, and miR-222) as Biomarkers of Endothelial Corpus Cavernosum Dysfunction in a Diabetic Alcoholic Murine Model.

Tiraboschi RB, Neto FSL, da Cunha Tirapelli DP, de Bessa J Jr, Miranda EP, de Assis Cirino ML, Tirapelli LF, Tucci S Jr, Molina CAF. Sex Med. 2021 Apr;9(2):100326. doi: 10.1016/j.esxm.2021.100326. Epub 2021 Mar 3. PMID: 33676226; PMCID: PMC8072178.

The authors aimed to investigate the expression of miR-15b, miR-16, miR-138, miR-221, and miR-222 in corpus cavernosum (CC) and peripheral blood in a rat model of endothelium dysfunction secondary to diabetes (DM) and alcohol consumption to assess potential endothelial lesion biomarkers. Twenty males Wistar rats were divided into 4 groups: control group (C), alcohol consumption group (A), diabetic group (D), diabetic-alcohol consumption group (D + A). The authors found that 3 miRNAs (miR-16, miR-221, and miR-222) were downregulated in the CC in the D+A group, while all 5 miRNAs were downregulated in the blood of D and D + A groups. In conclusion, miRNAs downregulation was identified in both CC and blood notably in DM associated with alcohol consumption animals (D + A), the greatest endothelial injury potential group.

Beneficial Effects of Human Umbilical Cord Blood Mononuclear Cells on Persistent Erectile Dysfunction After Treatment of 5-Alpha Reductase Inhibitor in Rats.

Oztekin CV, Yilmaz-Oral D, Kaya-Sezginer E, Kirlangic OF, Ozen FZ, Ozdal B, Topcu HO, Gur S. J Sex Med. 2021 May;18(5):889-899. doi: 10.1016/j.jsxm.2021.02.005. Epub 2021 Mar 27. PMID: 33785264.

Effects of human umbilical cord blood (HUCB) as a valuable source for stem cell-based therapies have not been studied in persistent post-5-alpha reductase inhibitors (5ARI) erectile dysfunction

(PPED). This study aimed to determine the effect of intracavernosal injection of HUCB mononuclear cells (MNCs) on ED associated with dutasteride treatment. Twenty five adult male Sprague-Dawley rats were divided into 5 groups (n = 5 per group): (i) control, (ii) 8-week dutasteride (0.5 mg/kg/day, in drinking water), (iii) 12-week dutasteride, (iv) 8-week dutasteride+HUCB-MNCs (1 × 106) and (v) 12-week dutasteride+HUCB-MNCs. HUCB-MNCs were administered intracavernosally after eight weeks of dutasteride treatment. Erectile responses in the dutasteride-treated groups were significantly decreased compared with controls, persisting after 4-wk of washout. HUCB-MNCs restored diminished intracavernosal pressure responses, acetylcholine-, sodium nitroprusside-, sildenafil-induced relaxations, and increased phenylephrine and electrical field stimulation (EFS)-induced contractions. Decreased EFS-induced relaxations in dutasteride-treated groups were not restored by HUCB-MNCs. Increased PDE5 and reduced nNOS expressions in dutasteride groups were restored by HUCB-MNCs in the 12-week dutasteride group. HUCB-MNCs reversed the decreased smooth muscle/collagen ratio in dutasteride-treated tissues. This study demonstrates the corrective potential of HUCB-MNCs on some persistent structural and functional deterioration caused by 5ARI treatment in rats, which may encourage further evaluation of HUCB-MNCs in men with PPED.

CXCL5 Cytokine Is a Major Factor in Platelet-Rich Plasma's Preservation of Erectile Function in Rats After Bilateral Cavernous Nerve Injury.

Wu YN, Liao CH, Chen KC, Chiang HS. J Sex Med. 2021 Apr;18(4):698-710. doi: 10.1016/j.jsxm.2020.12.016. Epub 2021 Mar 23. PMID: 33741291.

This study aimed to determine factors released from platelet-rich plasma (PRP) and explore their role in mediating preservation of erectile function (EF) in a rat model of cavernous nerve (CN) injury. Male Sprague-Dawley rats were used in this study. The authors determined the expression patterns of C-X-C motif chemokine ligand 5 (CXCL5) and receptors in the major pelvic ganglion (MPG) and corpus cavernosum via immunostaining. The PRP contained high levels of CXCL5. MPG neurons expressed CXCL5 and CXCR2. PRP intracavernous injection stabilized CXCR2 and increased CXCL5 expression in the MPG after BCNC, thus enhancing neuroprotection. CXCL5 injection improved BCNC-induced erectile dysfunction by preventing smooth muscle atrophy. This study provides evidence for the role of CXCL5 and CXCR2 as mediators of PRP effects in the preservation of EF after CN injury.

Caspase Signaling in ED Patients and Animal Models.

Martin S, Harrington DA, Ohlander S, Stupp SI, McVary KT, Podlasek CA. J Sex Med. 2021 Apr;18(4):711-722. doi: 10.1016/j.jsxm.2021.01.175. Epub 2021 Mar 9. PMID: 33707045; PMCID: PMC8068676.

The authors examined the mechanism of how apoptosis occurs in erectile dysfunction (ED) patients and cavernous nerve (CN) injury rat models to determine points of intervention for therapy development. Immunohistochemical and western analyses for caspase 3-cleaved, caspase-8 and caspase-9 (pro and active forms) were performed in corpora cavernosal tissue from Peyronie's, prostatectomy and diabetic ED patients (n = 33), penis from adult Sprague Dawley rats that underwent CN crush (n = 24), BB/WOR diabetic and control rats (n = 8), and aged rats (n = 9). Caspase 3-cleaved was observed in corpora cavernosa from Peyronie's patients and at higher abundance in prostatectomy and diabetic tissues. Apoptosis takes place primarily through the extrinsic (caspase 8) pathway in penis tissue of ED patients. In the CN crushed rat, caspase 3-cleaved was abundant from 1-9 days after injury, and apoptosis takes place primarily via the intrinsic (caspase 9) pathway. Caspase 9 was first observed and most abundant in a layer under the tunica, and after several days was observed in the lining of and between the sinuses of the corpora cavernosa. Caspase 8 was initially observed at low abundance in the rat corpora cavernosa and was not observed at later time points after CN injury. The authors concluded that apoptosis takes place primarily through the extrinsic caspase 8 dependent pathway in ED patients and via the intrinsic caspase 9 dependent pathway in commonly used CN crush ED models. This is an important consideration for study design and interpretation that must be taken into account for therapy development and testing of drugs.

Macrophage-Specific Toll Like Receptor 9 (TLR9) Causes Corpus Cavernosum Dysfunction in Mice Fed a High Fat Diet.

Priviero F, Calmasini F, Dela Justina V, Wenceslau CF, McCarthy CG, Webb RC. J Sex Med. 2021 Apr;18(4):723-731. doi: 10.1016/j.jsxm.2021.01.180. Epub 2021 Mar 16. PMID: 33741290; PMCID: PMC8068605.

Since obesity triggers an inflammatory process, the authors aimed to investigate the hypothesis that in obesity, Toll-like receptor 9 (TLR9) activation leads to increased TNF-α levels and impairment in corpus cavernosum (CC) reactivity. Four-week old male C57BL6 (WT) and TLR9 mutant (TLR9MUT) mice were fed a standard chow or high fat diet (HFD) for 12 weeks. Body weight and nonfasting blood glucose were analyzed. Contractile and relaxation responses of the CC were evaluated by electrical field stimulation and concentration response curves to phenylephrine and acetylcholine. After 12 weeks of HFD both WT and TLR9MUT mice had increased body weight and nonfasting blood glucose compared to standard chow. In the CC, acetylcholine-induced relaxation was not changed. This findings indicate that CC dysfunction observed in obesity is at least in part mediated by the production of TNF-α upon activation of TLR9 expressed in the macrophages.

Oral Administration of the p75 Neurotrophin Receptor Modulator, LM11A-31, Improves Erectile Function in a Mouse Model of Cavernous Nerve Injury.

Yin GN, Ock J, Limanjaya A, Minh NN, Hong SS, Yang T, Longo FM, Ryu JK, Suh JK. J Sex Med. 2021 Jan;18(1):17-28. doi: 10.1016/j.jsxm.2020.10.015. Epub 2020 Nov 24. PMID: 33243690.

This study aimed to investigate the therapeutic effect of oral administration of LM11A-31, a small molecule p75 neurotrophin receptor (p75NTR) ligand and proNGF antagonist, in a mouse model of bilateral cavernous nerve injury (CNI), which mimics nerve injury-induced erectile dysfunction after radical prostatectomy. 8-week-old male C57BL/6 mice were divided into sham operation and CNI groups. Each group was divided into 2 subgroups: phosphate-buffered saline and LM11A-31 (50 mg/kg/day). Erectile function was decreased in the CNI group (44% of the sham operation group), while administration of LM11A-31 led to a significant improvement of erectile function (70% of the sham operation group) in association with increased neurovascular content, including cavernous endothelial cells, pericytes, and neuronal processes. Immunohistochemical and Western blot analyses showed significantly increased p75NTR expression in the dorsal nerve of CNI mice, which was attenuated by LM11A-31 treatment. Protein expression of active PI3K, AKT, and endothelial nitric oxide synthase was increased, and cell death and c-Jun N-terminal kinase signaling was significantly attenuated after LM11A-31 treatment. The authors concluded that specific inhibition of the proNGF-p75NTR degenerative signaling via oral administration of LM11A-31 represents a novel therapeutic strategy for erectile dysfunction induced by nerve injury.

Culture and purification of SD rat corpus cavernosum endothelial cells by enzymatic digestion combined with mechanical extrusion and fixed-point digestion.

Chen Y, Qi T, Zhu SG, Li H, Feng JX, Zhang B, Li SX, Ma S, Ma Q, Chu QJ, Yang WT, Chen J. Andrologia. 2021 Jul 30:e14194. doi: 10.1111/and.14194. Epub ahead of print. PMID: 34328658.

The authors aimed to explore a new method of in vitro culture and purification of rat corpus cavernosum endothelial cells (CCECs). Male Sprague-Dawley rats' penile tissue were digested with elastase or collagenase combined with mechanical extrusion to isolate and culture the CCECs. The fixed-point digestion method was used to purify the primary cells. Following the digestion of the primary CCECs by elastase or collagenase coupled with mechanical extrusion, the cells were paving stone- and cobblestone-shaped over 10 days. The cell purity yielded in the second generation (P2) CCECs after using the fixed-point digestion method was significantly high. Compared with primary CCECs extracted by elastase digestion combined with the mechanical extrusion method, CCECs cultured by collagenase digestion yielded higher purity and a more stable morphology after fixed-point digestion and purification. Enzymatic digestion combined with mechanical extrusion and fixed-point digestion is a simple, economical method for in vitro culture and purification of CCECs, which is conducive to studying the pathophysiological mechanisms of endothelial dysfunction and erectile dysfunction.

Extracorporeal shock wave therapy combined with engineered mesenchymal stem cells expressing stromal cell-derived factor-1 can improve erectile dysfunction in streptozotocin-induced diabetic rats.

Shin D, Jeon SH, Tian WJ, Kwon EB, Kim GE, Bae WJ, Cho HJ, Hong SH, Lee JY, Kim SW. Transl Androl Urol. 2021 Jun;10(6):2362-2372. doi: 10.21037/tau-21-79. PMID: 34295723; PMCID: PMC8261440.

The objective of this study was to investigate whether extracorporeal shock wave therapy (ESWT) in combination with stromal cell-derived factor-1 expressing engineered mesenchymal stem cell (SDF-1 eMSC) therapy can have synergistic effects on erectile dysfunction (ED) in streptozotocin-induced diabetic (DM) rats. Fifty 8-week-old male Sprague-Dawley rats were randomly divided into five groups: (I) Normal group, (II) DM ED, (III) DM ED + ESWT group, (IV) DM ED + SDF-1 eMSC group, and (V) DM ED + ESWT + SDF-1 eMSC group. Each groups were treated with bilateral injections of SDF-1 eMSC or ESWT following the experiment protocol for eight weeks. The ratio of ICP/MAP was distinctly higher in the DM ED + ESWT + SDF-1 eMSC group than that in the DM ED group. Additionally, ESWT increased the intensity of SDF-1 expression in the corpus cavernosum. ESWT + SDF-1 eMSC treatment also induced neuronal nitric oxide synthase (nNOS) and NO/cGMP expression in the corpus cavernosum. Combined treatment of ESWT with SDF-1 eMSC treatment could be used as a potential and effective synergistic treatment for DM ED.

Transplantation of Human Gingiva-Derived Mesenchymal Stem Cells Ameliorates Neurotic Erectile Dysfunction in a Rat Model.

Wu J, Chen Z, Zhong F, Yang W, Ouyang X, Ma X, Zheng S, Wei H. Front Bioeng Biotechnol. 2021 Jun 21;9:630076. doi: 10.3389/fbioe.2021.630076. PMID: 34235136; PMCID: PMC8255925.

The authors injected the human gingiva-derived mesenchymal stem cells (hGMSCs) around the bilateral major pelvic ganglia (MPG) in a rat model of cavernous nerve injury (CNI) and evaluated their efficacy. The results showed that treatment of hGMSCs could significantly promote the recovery of erectile function, enhance smooth muscle and endothelial content, restore neuronal nitric oxide synthase (nNOS) expression, and attenuate cell apoptosis in penile tissue. Moreover, penile fibrosis was significantly alleviated after hGMSC administration. In addition, potential mechanism exploration indicated that hGMSCs might exert its functions via skewed macrophage polarity from M1 toward M2 anti-inflammatory phenotype.

Inhibition of inducible nitric oxide synthase improved erectile dysfunction in rats with type 1 diabetes.

Liu L, Wang X, Liu K, Kang J, Wang S, Song Y, Zhou K, Yi L, Liu X. Andrologia. 2021 Sep;53(8):e14138. doi: 10.1111/and.14138. Epub 2021 Jun 16. PMID: 34137064.

The purpose of this study was to investigate the role of iNOS in diabetes mellitus erectile dysfunction (DMED). The authors developed a type 1 diabetes mellitus rat model using streptozotocin and selected those that developed DMED. Then, they injected these rats with the 1400W, an iNOS inhibitor, for 10 weeks and subsequently assessed their ED. Lastly, they performed various molecular studies and histopathological analyses of penile tissues collected from these rats after the experiments. Through the histopathological studies,the authors also found that the treatment restored the ratios of the smooth muscle to collagen fibres, delayed the development of microvascular injury and alleviated the oxidative stress caused by hyperglycaemia.

HYPOGONADISM

Androgen-dependent miR-125a-5p targets LYPLA1 and regulates global protein palmitoylation level in late-onset hypogonadism males.

Qu M, Zhao Y, Qing X, Zhang X, Li H. J Cell Physiol. 2021 Jun;236(6):4738-4749. doi: 10.1002/jcp.30195. Epub 2020 Dec 7. PMID: 33284463.

This study demonstrated that plasma miR-125a-5p was upregulated after testosterone supplementation in both late-onset hypogonadism (LOH) patients and castrated mice, and positively associated with the testosterone concentrations, suggesting direct regulation of miR-125a-5p expression by testosterone. Androgen response element in the promoter of miR-125a-5p was subsequently identified. Target gene screening and confirmation verified that LYPLA1, encoding acyl-protein thioesterase 1 which catalyzed protein depalmitoylation process, was a target gene of miR-125a-5p. The results suggested that testosterone could regulate global palmitoylation level through miR-125a-5p/LYPLA1 signaling pathway.

Morphometric analysis and redox state of the testicles in nandrolone decanoate and swimming treated adult male rats.

Sretenovic J, Joksimovic Jovic J, Srejovic I, Zivkovic V, Mihajlovic K, Labudovic-Borovic M, Trifunovic S, Milosevic V, Lazic D, Bolevich S, Jakovljevic V, Milosavljevic Z. Basic Clin Androl. 2021 Jul 15;31(1):17. doi: 10.1186/s12610-021-00134-8. PMID: 34261436; PMCID: PMC8281612.

The aim of this study was to investigate the effects of four-week administration of nandrolone decanoate and swimming training alone or in combination on morphometric parameters, androgen receptor (AR) and redox state in testicle tissue. The study included Wistar albino male rats, 10 weeks old, classified into 4 groups: control (T-N-), nandrolone (T-N+), swimming training (T+N-) and swimming training with nandrolone (T+N+). The isolated testicles were measured, left testicles were routinely processed for histological analysis, while right testicles were homogenized and prepared for the analysis of the following oxidative stress biomarkers: index of lipid peroxidation (TBARS), nitrites, catalase, superoxide dismutase

(SOD), and reduced glutathione (GSH). Diameter, as well as cross-section area of seminiferous tubules were decreased by 10 % and 21 % (respectively) in the T-N+ group and by 15% and 41 % (respectively) in the T+N+ group compared to control. Interstitium of the testicles was decreased in all experimental groups. Reduction of immunoreactivity of AR in T-N+ group was 22 %, in T+N+ group was 9 % compared to control. TBARS levels were increased in T+N- and T+N+ groups. Swimming alone or combined with nandrolone decreased the level of GSH compared to control. SOD activity was decreased in T-N+ and T+N+ groups compared to control.

EJACULATION DISORDERS

Central Mechanisms of Apomorphine and m-Chlorophenylpiperazine on Synergistic Action for Ejaculation in Rats.

Yoshizumi M, Yonezawa A, Kimura Y, Watanabe C, Sakurada S, Mizoguchi H. J Sex Med. 2021 Feb;18(2):231-239. doi: 10.1016/j.jsxm.2020.10.014. Epub 2020 Nov 23. PMID: 33243689.

The combination of the dopamine (DA) receptor agonist apomorphine and the 5-hydroxytryptamine (5-HT2) receptor agonist m-chlorophenylpiperazine (m-CPP) in rats potently and selectively facilitates the ejaculatory response through activation of D2-like and 5-HT2C receptors, respectively. The aim of this study was to clarify the target level of the proejaculatory effects induced by combination of these agonists. Intrathecal m-CPP (10 μg), but not intracerebroventricular m-CPP, evoked the synergistic effects on ejaculation when used in combination with systemically administered apomorphine (0.1 mg/kg, subcutaneous). Moreover, the synergy between m-CPP and apomorphine was completely abolished by the intrathecal 5-HT2C receptor antagonist SB242084 (10 μg). Intrathecal or intracerebroventricular apomorphine (1-10 μg) evoked proejaculatory effects in combination with systemically administered m-CPP (0.3 mg/kg, intraperitoneal). The selective peripherally acting D2-like receptor agonist carmoxirole did not evoke ejaculation when used in combination with m-CPP. Furthermore, isolated rat seminal vesicles were completely insensitive to the combination of apomorphine and m-CPP.These results indicated that the synergistic effects of the drugs on ejaculation were induced at the central level but not at peripheral sites. This findings also suggested that the 5-HT2C receptor mediated the stimulation of the spinal ejaculatory pattern generator and was synergistically potentiated by the spinal DA receptor and that activation of the supraspinal DA receptor was also involved in mediating these synergistic effects.

Spinal Cord Injury Causes Reduction of Galanin and Gastrin Releasing Peptide mRNA Expression in the Spinal Ejaculation Generator of Male Rats.

Wiggins JW, Sledd JE, Coolen LM. Front Neurol. 2021 Jun 22;12:670536. doi: 10.3389/fneur.2021.670536. PMID: 34239493; PMCID: PMC8258150.

It was previously demonstrated that spinal contusion injury in male rats caused reduction of GRP-immunoreactivity, but not galanin-immunoreactivity in lumbar spinothalamic (LSt) cells, indicative of reduced gastrin releasing peptide (GRP) levels, but inconclusive results for galanin. The current study further tests the hypothesis that contusion injury causes a disruption of GRP and galanin mRNA in LSt cells. Male rats received mid-thoracic contusion injury and galanin and GRP mRNA were visualized 8 weeks later in the lumbar spinal cord using fluorescent in situ hybridization. Spinal cord injury (SCI) significantly reduced GRP and galanin mRNA in LSt cells. Galanin expression was higher in LSt cells compared to GRP. However, expression of the two transcripts were positively correlated in LSt cells in both sham and SCI animals, suggesting that expression for the two neuropeptides may be co-regulated. GRP and galanin are both essential for triggering ejaculation and thus such reduction may contribute to ejaculatory dysfunction following SCI in rats.

Physiological and pharmacological impact of oxytocin on epididymal propulsion during the ejaculatory process in rodents and men.

Stadler B, Nowell CJ, Whittaker MR, Arnhold S, Pilatz A, Wagenlehner FM, Exintaris B, Middendorff R. FASEB J. 2021 Jun;35(6):e21639. doi: 10.1096/fj.202100435R. PMID: 34041782.

The authors investigated the effect of oxytocin (suggested to exert effects during ejaculation) on defined segments of the rat and human epididymis using live imaging. The results indicate that it is the very last part of the epididymis, segment 19 (S19) in rat and likewise segment 9 in human, which responds in a uniquely strong and rapid manner to oxytocin (similar to noradrenaline). The reaction of S19 to oxytocin was concentration-dependent and could be inhibited by pretreatment with oxytocin antagonists (atosiban and cligosiban), but not with an arginine vasopressin 1A antagonist (SR49059). In both rat and human tissue, pretreatment with the alpha-1 adrenoreceptor antagonist tamsulosin inhibited the response to noradrenaline, whereas the effect of oxytocin was unimpaired. This data (from men and rodents) strongly suggest that the hormone oxytocin is involved in the ejaculatory process. Thus, oxytocin-based medications might be a promising non-adrenergic treatment option for ejaculatory disorders.

PEYRONIE'S DISEASE

RNA-sequencing profiling analysis of pericyte-derived extracellular vesicle-mimetic nanovesicles-regulated genes in primary cultured fibroblasts from normal and Peyronie's disease penile tunica albuginea.

Yin GN, Piao S, Liu Z, Wang L, Ock J, Kwon MH, Kim DK, Gho YS, Suh JK, Ryu JK. BMC Urol. 2021 Aug 6;21(1):103. doi: 10.1186/s12894-021-00872-x. PMID: 34362357; PMCID: PMC8344132.

Extracellular vesicle (EV)–mimetic nanovesicles (NVs) have attracted attention regarding intercellular communication between cells in the field of fibrosis. However, the global gene expression of pericyte-derived EV–mimetic NVs (PC–NVs) in regulating fibrosis remains unknown. The authors used RNA-sequencing technology to investigate the potential target genes regulated by PC–NVs in primary fibroblasts derived from human Peyronie Disease (PD) plaque. Human primary fibroblasts derived from normal and PD patients was cultured and treated with cavernosum pericytes isolated extracellular vesicle (EV)–mimetic nanovesicles (NVs). A total of 4135 genes showed significantly differential expression in the normal fibroblasts, PD fibroblasts, and PD fibroblasts treated with PC–NVs. However, only 91 contra-regulated genes were detected among the three libraries. In conclusion, the gene expression profiling results suggested that these validated genes may be good targets for understanding potential mechanisms and conducting molecular studies into PD.

Mechanical characterization of fibrotic and mineralized tissue in Peyronie's disease.

Brady L, Stender CJ, Wang YN, Schade GR, Maxwell AD, Wessells H, Ledoux WR. Int J Impot Res. 2021 May 25. doi: 10.1038/s41443-021-00439-2. Epub ahead of print. PMID: 34035467.

This work aimed to establish mechanical testing methodology and characterize pathological tissue mechanics of Peyronie's disease. Tunica albuginea was obtained from patients (n = 5) undergoing reconstructive surgery for Peyronie's disease, sectioned into test specimens (n = 12) and imaged with micro-computed tomography (μCT). A tensile testing protocol was developed based on similar soft tissues. Correlation of mechanical summary variables (force, displacement, stiffness, work, Young's modulus, ultimate tensile stress, strain at ultimate tensile stress, and toughness) and μCT features were assessed. Mineralization volume was not correlated with mechanical parameters. Empirically hard tissue had higher ultimate tensile stress. Failure mechanisms and strain patterns differed between mineralized and non-mineralized specimens. Size, shape, and quantity of mineralization may be more important in determining Peyronie's disease plaque behavior than presence of mineralization alone, and single summary variables like modulus may not fully describe mechanical behavior.

Single-cell Transcriptomics Uncover a Novel Role of Myeloid Cells and T-lymphocytes in the Fibrotic Microenvironment in Peyronie's Disease.

Milenkovic U, Boeckx B, Lambrechts D, Janky R, Hatzichristodoulou G, van Renterghem K, Gevaert T, Cellek S, Bivalacqua TJ, De Ridder D, Albersen M. Eur Urol Focus. 2021 May 4:S2405-4569(21)00118-8. doi: 10.1016/j.euf.2021.04.012. Epub ahead of print. PMID: 33962884.

This work aimed to investigate the immunological signature of plaques from Peyronie's disease (PD) patients using immunohistochemistry (IHC) and single-cell RNA sequencing (scRNA-Seq). Tunica albuginea biopsy was performed in patients undergoing penile surgery for either PD (n = 12) or plication or penile cancer (control, n = 6). IHC revealed the presence of myeloid dendritic cells (DCs; CD68+, TLR4+, CD206+), cytotoxic T lymphocytes (CTLs; CD3+, CD8+), and B lymphocytes (CD20+) in PD plaques, which were absent in controls. scRNA-Seq yielded results for 3312 PD and 5658 control cells. Cell clusters contained fibroblasts (COL1A2+), myofibroblasts (COL1A2+, ACTA2+), smooth muscle cells (ACTA2+, DES+), endothelial cells (VWF+), myeloid cells (CD14+), T lymphocytes (CD3D+), and neutrophils (ALPL+). Myeloid cell subclustering showed infiltration of monocyte-derived cells; control tissue contained classical DCs and resident macrophages. This data suggest that even in the chronic PD stage (painless and stable curvature) there is a sustained inflammatory reaction. While vascularisation and collagen production are elevated, the inflammation is driven by specialised monocyte-derived CTL and MAIT cells.

ONCOLOGY

Oxaliplatin, an Anticancer Agent, Causes Erectile Dysfunction in Rats due to Endothelial Dysfunction.

Kataoka T, Mori T, Suzuki J, Kawaki Y, Kito Y, Hotta Y, Kawade Y, Maeda Y, Kimura K. J Sex Med. 2021 Aug;18(8):1337-1345. doi: 10.1016/j.jsxm.2021.06.004. Epub 2021 Jul 17. PMID: 34281797.

This study aimed to investigate erectile function in an animal model after administration of the anticancer agent oxaliplatin (L-OHP). Male Wistar/ST rats were divided into 2 groups: L-OHP rats (n = 21), which were intravenously administered L-OHP (4 mg/kg; twice a week for 4 weeks), and Control rats (n = 21), which were injected with the same volume of 5% glucose solution, using the same dosing schedule. At the end of the study period, erectile function was evaluated by measuring intracavernous pressure (ICP) and mean arterial pressure (MAP) after cavernous nerve stimulation (n = 9–10). Endothelial function was evaluated with an isometric tension study using corpus cavernosum strips (n = 11). Western blot analysis was used to assess neuronal nitric oxide (nNOS) and endothelial NO synthase (eNOS) protein levels (n = 7). The L-OHP group had a significantly lower ICP:MAP ratio than the control group ($P < .05$). Compared to the Control group, the L-OHP group exhibited significantly lower responses to ACh and eNOS protein levels and significantly higher inflammatory biomarker levels. The results based on this animal model indicate that use of the anticancer agent L-OHP should be considered as a risk factor for ED occurring via reduction of NO bioavailability in humans; our results provide possible treatment strategies for maintaining the erectile function of cancer survivors.

ORGASM/ SEXUAL DESIRE

Sexual Motivation and Sexual Reward in Male Rats are Attenuated by the Gonadotropin-Releasing Hormone Receptor Antagonist Degarelix.

Hawley WR, Kapp LE, Dingle CM, Dufala HA, Green PA, Barnes JL, Barwell JL. J Sex Med. 2021 Feb;18(2):240-255. doi: 10.1016/j.jsxm.2020.11.004. Epub 2021 Jan 6. PMID: 33419705.

The aim of this study was to examine the effects of a single administration of the gonadotropin-releasing hormone receptor antagonist, degarelix, on sexual incentive motivation (SIM), sexual reward, consummatory sexual behaviors, anxiety-like behavior, and androgen receptor signaling in male rats, and to determine if sexual stimulation attenuates the effects of degarelix on SIM. Rats treated with degarelix exhibited lower levels of SIM. In rats treated with degarelix, contact with a female immediately before SIM testing increased activity, but not SIM. Treatment with degarelix reduced the rewarding aspects of sexual behavior, as well as most aspects of copulatory ability and sexual performance.

FEMALE SEXUALITY

Changes of Apomorphine-Induced Vaginal Hemodynamics in an Ovariectomized Rat Model Using Near-Infrared Spectroscopic Probe.

Jeong H, Lee HS, Seong M, Baek J, Park K, Kim JG. J Sex Med. 2021 Aug.18(8):1328-1336. doi: 10.1016/j.jsxm.2021.05.012. Epub 2021 Jul 8. PMID: 34247951.

This study aimed to investigate the longitudinal changes in female sexual arousal response induced by apomorphine (APO) administration in the ovariectomized rat using near-infrared spectroscopy (NIRS) probe.

To elicit sexual arousal, APO was administered subcutaneously to animals (n = 6) before and after ovariectomy, and the changes in oxyhemoglobin (OHb), deoxyhemoglobin (RHb), total hemoglobin (THb) concentration, and temperature on the vaginal wall after APO administration were monitored bi-weekly for 8 weeks. APO administration caused the increase of vaginal OHb and RHb concentration but a decrease in temperature. The amplitude of OHb, RHb, and THb increase induced by APO gradually decreased over 8 weeks after ovariectomy while the decrease in vaginal temperature became profound. A comparison between the parameters measured from the NIRS probe and the others (estradiol level,

amount of vaginal secretion, and body weight) proved that the NIRS has the potential as a monitoring tool to evaluate female sexual arousal response.

Immunohistochemical Investigation of Autonomic and Sensory Innervation of Anterior Vaginal Wall Female Periurethral Tissue: A Study of the Surgical Field of Mid-Urethral Sling Surgery Using Cadaveric Simulation.

Giovannetti O, Tomalty D, Gaudet D, Clohosey D, Forster A, Monaghan M, Harvey MA, Johnston S, Komisaruk B, Goldstein S, Hannan J, Goldstein I, Adams MA. J Sex Med. 2021 Jul;18(7):1167-1180. doi: 10.1016/j.jsxm.2021.05.002. Epub 2021 Jun 24. PMID: 34176756.

Anterior vaginal wall-female periurethral tissue (AVW-FPT) likely contains autonomic and sensory innervation involved in the female sexual response, and injury to these nerves may result from mid-urethral sling (MUS) implantation. This study aimed to characterize, using fresh cadaveric tissue, autonomic and sensory nerves in AVW- FPT using immunohistochemistry (IHC), and to assess their proximity to an implanted MUS. AVW-FPT was excised from four fresh cadavers. IHC of AVW-FPT using protein gene product 9.5 (PGP9.5), a general nerve stain, revealed innervation throughout the region targeted by the MUS implantation. More specifically, immunoreactivity for both autonomic (tyrosine hydroxylase, TH) and sensory (Nav1.8 and S100ß) nerves were found in close proximity (<1 mm) to the implanted MUS. Combining the IHC findings with the surgical simulation of the MUS implantation revealed the potential for damage to both autonomic and sensory nerves as a direct result of the MUS procedure.

Overexpressing miR-122-5p Inhibits the Relaxation of Vaginal Smooth Muscle in Female Sexual Arousal Disorder by Targeting Vasoactive Intestinal Peptide Receptor 1.

Cong S, Gui T, Shi Q, Zhang J, Feng J, Pan L, Ma J, Zhang A. Sex Med. 2021 Aug;9(4):100390. doi: 10.1016/j.esxm.2021.100390. Epub 2021 Jul 8. PMID: 34246178; PMCID: PMC8360939.

The aim if this study was to investigate the specific function of miR-122-5p in Female sexual arousal disorder (FSAD). The authors verified that women with FSAD had higher miR-122-5p and lower vasoactive intestinal peptide receptor 1 (VIPR1) protein. Then overexpressing miR-122-5p decreased relaxation of rat vaginal smooth muscle cells (SMCs), which was manifested as a contractile morphology of cells, an increased intracellular free Ca2+ concentration, and lower cAMP concentration and PKA activity. The authors concluded thatvmiR-122-5p regulates the relaxation of vaginal SMCs in FSAD by targeting VIPR1, ulteriorly providing an underlying diagnostic and therapeutic target for FSAD.

GENDER INCONGRUENCE

Implications of the Estrogen Receptor Coactivators SRC1 and SRC2 in the Biological Basis of Gender Incongruence.

Ramírez KDV, Fernández R, Delgado-Zayas E, Gómez-Gil E, Esteva I, Guillamon A, Pásaro E. Sex Med. 2021 Jun;9(3):100368. doi: 10.1016/j.esxm.2021.100368. Epub 2021 May 26. PMID: 34049263; PMCID: PMC8240342.

This study aimed to to analyze the implication of the estrogen receptor coactivators SRC-1, SRC-2, and SRC-3 in the genetic basis of gender incongruence. The authors analysed 157 polymorphisms located at the estrogen receptor coactivators SRC-1, SRC-2, and SRC-3, in 94 transgender versus 94 cisgender individuals. They found significant differences in 8 polymorphisms that correspond to 5.09% of the total. Three were located in SRC-1 and 5 in SRC-2. The SRC-1 haplotypes CGA and CGG and the SRC-2 haplotypes GGTAA and GGTAG were overrepresented in the transgender population. In conclusion, the coactivators SRC-1 and SRC-2 could be considered as candidates for increasing the list of potential genes for gender incongruence.

7

Have you read? Best of the Best: Clinical Research

Pereira, B.J.
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COVID-19 AND SEXUAL MEDICINE

Sansone A, Mollaioli D, Ciocca G, Colonnello E, Limoncin E, Balercia G and Jannini EA. "Mask Up to Keep It Up": Preliminary Evidence of the Association Between Erectile Dysfunction and COVID-19. Andrology 2021; 9: 1053-105.

ED as the hallmark of endothelial dysfunction, could be a short- or long-term complication of COVID-19. Additionally, being ED a clinical marker and predictor of non-communicable chronic diseases, particularly cardiovascular, subjects with ED could potentially have a higher risk of contracting COVID-19. This article aims to to investigate the prevalence of ED among subjects with a reported diagnosis of COVID-19 and to measure the association of COVID-19 and ED. Data from the Sex@COVID online survey (between April 7 and May 4, 2020, Italy) to retrieve a sample of Italian male sexually active subjects with reported SARS-CoV-2 infection. A matching sample of COVID-19-negative male sexually active subjects was also retrieved using propensity score matching in a 3:1 ratio. 100 subjects were included in the analysis (25 COVID-positive; 75 COVID-negative). The prevalence of ED, measured with the SHIM, was significantly higher in the COVID+ group (28% vs. 9.33%; p = 0.027). Logistic regression models confirmed a significant effect of COVID-19 on the development of ED, independently of other variables affecting erectile function, such as psychological status, age, and BMI. Likewise, subjects with ED were more likely to have COVID-19, once corrected for age and BMI. On top of well-described pathophysiological mechanisms, there is preliminary evidence in a real-life population of ED as a risk factor of developing COVID-19 and possibly occurring because of COVID-19. Universal vaccination against the COVID-19 and the personal protective equipment could possibly have the added benefit of preventing sexual dysfunctions.

Mollaioli D, Sansone A, Ciocca G, et al. Benefits of Sexual Activity on Psychological, Relational, and Sexual Health During the COVID-19 Breakout. J Sex Med 2021;18:35e49. The COVID-19-related lockdown has profoundly changed human behaviors and habits, impairing general and psychological well-being. A case-control study was performed through a web-based survey and comparing subjects of both genders with (group A, N= 2,608) and without (group B, N= 4,213) sexual activity during lockdown. Anxiety and depression scores were significantly lower in subjects sexually active during lockdown. Logistic regression models showed that lack of sexual activity during lockdown was associated with a significantly higher risk of developing anxiety and depression (OR: 1.32 and 1.34, respectively). This study elucidated the protective role of sexual activity for psychological distress, as well for relational and sexual health. Main limitations were the web-based characteristics of the protocol and the retrospective nature of prelockdown data on psychorelational and sexual health of subjects recruited. COVID-19 lockdown dramatically impacted on psychological, relational, and sexual health of the population. In this scenario, sexual activity played a protective effect, in both genders, on the quarantine-related plague of anxiety and mood disorders.

MEN'S HEALTH

Towe M, El-Khatib F, Osman M et al. "Doc, If It Were You, What Would You Do?": A Survey of Men's Health Specialists' Personal Preferences Regarding Treatment Modalities. Int J Impot Res 2021; 33: 303–310.

Men's Health is a urological subspecialty that is at the forefront of innovation, but little data exist evaluating the attitudes that andrologists have toward the current treatment modalities available for managing Men's Health conditions. A survey of 37 questions asking what providers would choose as treatment for common conditions was distributed online via Survey Monkey to members of the SMSNA and ESSM. A total of 115 respondents completed the survey after an initial screening question. For erectile dysfunction (ED), 40%, 38%, and 33% of providers indicated that they would use tadalafil daily, tadalafil on demand, or sildenafil on demand, respectively, as first-line PDE5i therapy. Furthermore, a total of 74% would elect to undergo LiSWT therapy [67%], PRP injections [15%], and stem cell injections [15%]. Sex/behavioral therapy was preferred for both premature (36%) and delayed (52%) ejaculation. Approximately 44% of respondents indicated that they would undergo Collagenase Clostridium Histolyticum injections for Peyronie's Disease in the acute phase. In the setting of hypogonadal symptoms with borderline low total testosterone levels (300–400 ng/dL), 69% of respondents would pursue testosterone therapy. The prostatic lift procedure was the preferred procedure for men seeking symptom resolution

with preservation of ejaculatory function. Many Men's Health specialists would pursue the least invasive options before considering procedural intervention for any given condition. Providers may shift their treatment preferences toward newer treatment modalities as longer term data become available.

MALE SEXUAL (DYS)FUNCTION

Bañuelos Marco B, García Heil JL. Circumcision in Childhood and Male Sexual Function: A Blessing or a Curse? Int J Impot Res 2021; 33: 139-148.

Male circumcision (MC) is the first planned surgical procedure ever performed. Nowadays many of these procedures are not necessarily carried out in a medical environment, therefore the real number remains unknown but it is estimated that one third of the men are circumcised. Some authors argue the negative impact of MC on men psychology and sexual life, but objective data are lacking. A non-systematic narrative review was performed including articles between 1986 and 2019. Although many authors support the hypothesis that circumcision status has an impact on sexual functioning, a negative outcome has not yet been entirely proven. Circumcision might affect how men perceive their body image, and consequently affect their sexual life. We should consider this when analyzing the literature about MC and sexual dysfunction, as many of the results are based on specific populations with different attitudes towards this procedure. Sexual function consists of many elements that not only relate to measurable facts such as anatomy, somatosensory and histology. An objective evaluation of the impact of circumcision on sexuality is still challenging, as it affects a wide variety of people that confront sexuality differently due to their sociocultural and historical background. Therefore, individuals can either perceive their circumcision status as a blessing or a curse depending on the values and preferences of the different communities or social environments where they belong.

Capogrosso P, Jensen CFS, Rastrelli G, et al. Male Sexual Dysfunctions in the Infertile Couple – Recommendations From the European Society of Sexual Medicine (ESSM). Sex Med 2021; 9: 100377.

Sexual dysfunctions (SDs) have been frequently reported among male partners of infertile couples due to psychogenic, relational and/or organic issues related with the inability to conceive. Likewise, male infertility (MI) could be a consequence of sexual dysfunctions. This article aims to review the evidence on the prevalence and treatment of male SDs in men of infertile couples and provide clinical recommendations on behalf of the ESSM. ED has been reported in 9% to 62% of male partners of infertile couples, with severe impairment observed in only 1% to 3% of ED cases. Moreover, worse semen parameters have been associated with greater ED severity. PDE5is can be safely used to treat ED among patients seeking fatherhood. Male partners of infertile couples are at higher risk of PE. Retrograde ejaculation (RE) and anejaculation are a cause of MI and can be managed with electroejaculation (EEJ) or penile vibratory stimulation (PVS) or, alternatively, with oral treatments, however the latter with limited documented success. Low sexual desire has been reported by one third of men of infertile couples. In conclusion, ED could significantly affect male partners of infertile couple; PDE5is should be suggested to ensure an effective and satisfactory sexual relationship of the couple. Anejaculation and RE should be considered as a possible cause of MI and treated accordingly. Low sexual desire is frequently reported among men of infertile couple and could be a symptom of other systemic conditions or psychological distress.

ERECTILE DYSFUNCTION

Nunes AP, Seeger JD, Stewart A, et al. Cardiovascular Outcome Risks in Patients With Erectile Dysfunction Co-Prescribed a Phosphodiesterase Type 5 Inhibitor (PDE5i) and a Nitrate: A Retrospective Observational Study Using Electronic Health Record Data in the United States. J Sex Med 2021; XX: XXX–XXX.

PDE5i are first-line therapy for ED. Approximately 1–4% of PDE5i recipients co-possess nitrates, despite this combination potentially producing clinically significant hypotension. Real-world data in these patients and insights into prescriber rationales for co-prescription are limited. This study investigated whether PDE5i and nitrate co-possession is associated with increased rates of CV outcomes. Adult males with ED and PDE5i prescription and males with nitrate prescription were identified from a U.S. electronic health record database (2012–2016). Quantitative comparisons were made between patients with ED and co-possession (ED + PDE5i + nitrate), only nitrate possession (ED + nitrate and nitrate only [with- out ED]), and only PDE5i possession (ED + PDE5i). Over 168,000 patients had ≥1 PDE5i prescription (»241,000 possession periods); >480,000 patients had ≥1 nitrate prescription (»486,000 possession periods); and 3,167 patients had 3,668 co-possession

periods. Non-significantly different or lower rates of CV outcomes were observed for co-possession periods vs ED + nitrate and nitrate only periods. Most CV outcome rates were non-significantly different between co-possession and ED + PDE5i periods (myocardial infarction, hospitalized unstable angina and fainting were higher with co-possession). From qualitative assessment of patient records with co-possession, 131 of 252 (52%) documented discussion with a physician regarding co-possession; 69 of 131 (53%) warned or instructed on safely managing these contraindicated medications. Findings from this real-world study indicate that co-possession of nitrate and PDE5i prescriptions is not associated with increased rates of CV outcomes, relative to possession of nitrates alone. Co-exposure of PDE5i and nitrates should continue to be avoided; however, co-possession of PDE5i and nitrate prescriptions is not necessarily associated with increased CV risk. Co-possession can be successfully managed in suitable circumstances.

EJACULATORY DYSFUNCTION

Reisman, Y. Clinical Experience with Post-Orgasmic Illness Syndrome (POIS) Patients – Characteristics and Possible Treatment Modality. Int J Impot Res 2021; 33: 556–562.

Post-orgasmic illness syndrome (POIS) is a rare condition that includes a cluster of post-ejaculatory symptoms with debilitating physical and psychological consequences. The prevalence and incidence of POIS remain unknown as well as the pathophysiology of the syndrome, and there are no well-studied recognized treatment modalities. The current retrospective observational study describes a series of 14 highly selected patients who were actively looking for medical help as POIS has a significant effect on patients and partners. Mean age was 34.07 ± 6.65 years. The majority of patients had only one symptom in common – extreme fatigue. The most prevalent complaints were head pressure/heaviness, nose congestion and muscle tension; all patients suffered from more than one symptom. POIS started on average within 30 min of ejaculation and lasted for 3.5 days. The patients reported emotional and psychosocial burden of their symptoms, which also influence their partner and relationships. Immunoglobulin-E measurements did not show elevated levels and/or significant increase within 24 h after ejaculation. Silodosin, a highly selective alpha1A-blocker, which actually causes anejaculation, was effective treatment in 57% of the patients.

FEMALE SEXUAL HEALTH

Padoa A, Glick Fishman N, Tsviban A et al. Vaginal Postcoital Injuries Requiring Surgical Intervention: A Case Series and Literature Review. Int J Impot Res 2021; 33: 110-117.

This single-center case series describes clinical features and management of women who required surgical repair of vaginal injuries following consensual intercourse. Between January 2008 and December 2017, 20 women underwent hemostatic suturing for vaginal injuries following intercourse. Mean age was 27.6 ± 12.5 (range, 16–63) years, 5 (25%) women were parous, 13 (65%) women used no contraception, and 1 (5%) used birth control pills. Three patients (15%) were postmenopausal. Eight injuries (40%) occurred following first-time intercourse, two (10%) occurred after intercourse with a new partner. Median time from bleeding onset to admission was 12h (range, 2–24h) . One patient (5%) was hemodynamically unstable and required treatment with packed cells. Median time from admission to surgery was 56 (range, 15–540) min. The laceration site was identified at the vaginal fornix in nine (45%) patients, at mid-vagina in four (20%), at the hymenal ring, or the posterior fourchette in six (30%). Tear of a longitudinal vaginal septum was identified in one patient (5%). To conclude, vaginal postcoital injuries are a rare occurrence, nevertheless they may involve significant blood loss and therefore require prompt evaluation and treatment. Once the patient is hemodynamically stable, psychosexual assessment and support should be offered to the patient and her partner.

ONCOSEXOLOGY

Svanström Röjvall A, Buchli C, Flöter Radestad A, et al. Impact of Androgens on Sexual Function in Women With Rectal Cancer – A Prospective Cohort Study. J Sex Med 2021; 18:1374-1382.

Women treated for rectal cancer are at risk of sexual dysfunction and impaired ovarian androgen production. This prospective study aims to investigate a possible association between serum levels of endogenous androgens and sexual function in women with rectal cancer. Women diagnosed with stage I–III rectal cancer were consecutively included and prospectively followed. The primary outcome measure was the mean change observed in the FSFI total score when the serum androgen levels changed with one unit. Secondary

outcomes were the corresponding mean changes in the FSFI domain scores: sexual desire, arousal, lubrication, orgasm, satisfaction, and pain/discomfort. In the 99 participants, the median FSFI total score decreased from 21.9 (range 2.0 – 36.0) to 16.4 (3.5 – 34.5) and 11.5 (2.0 to 34.8) at 1 and 2-years follow-up. After adjustment for age, partner, psychological well-being, preoperative (chemo)radiotherapy, and surgery, total testosterone and androstenedione were significantly associated with FSFI total score. Testosterone was significantly associated with the FSFI-domains lubrication and orgasm, free testosterone with lubrication, androstenedione with all domains except desire and satisfaction, and dehydroepiandrosterone sulphate with none of the domains. In conclusion, testosterone and androstenedione were associated with sexual function in female rectal cancer patients. The results are of interest for future intervention studies and contribute to the understanding of sexual problems, which is an essential component of the rehabilitation process in pelvic cancer survivors.

BEHAVIOR

Flesia L, Fietta V, Foresta C, Monaro M. "What Are You Looking For?" Investigating the Association Between Dating App Use and Sexual Risk Behaviors. Sex Med 2021; 9: 100405.

This article aims to investigate the association between dating app use and sexual risk behaviors since evidence is still scant and inconclusive. 1.278 Italian respondents completed an online questionnaire assessing demographics, motives and patterns of dating app use, sexual behaviors and sexually transmitted infections (STIs) diagnoses. Active users, even more than former app users, were more likely to report risky behaviors and STI diagnoses than non-users ($x2 = 26.37$, $P < .001$). Installing the apps to find friends or romantic partners was associated with less protected and unprotected inter-
courses. Installing the apps to find sexual partners predicted higher odds of unprotected sexual activity, hook-ups and STIs diagnoses. Accessing apps more frequently and more years of usage was associated with reporting risky sexual behaviors and STI diagnoses among active users.

SURGERY

Falcone M, Blecher G, Anfosso M, Christopher AN, Ralph DJ. Total Phallic Reconstruction in the Genetic Male. Eur Urol 2021; 79: 684-691

This is a large retrospective tertiary referral centre analysis of a series of genetic male patients with penile insufficiency (PI) either due to congenital micropenis, or from traumatic or surgical amputation was conducted. Radial artery forearm free flap (RAFFF) was conducted as a multistaged procedure: (1) Total phallic reconstruction (TPR), (2) glans sculpting with second stage urethroplasty when indicated, and (3) penile prosthesis implantation.

A total of 108 patients were enrolled. The median age was 32.5 yr and median follow-up was 78.5 mo. A primary anastomotic urethroplasty was performed in 90 patients (83.4%) and a staged procedure in the remainder. Four patients experienced an acute arterial thrombosis, leading to complete loss of the phallus in two. Immediate surgical exploration saved the flap in two cases of venous thrombosis. Urethral complication occurred in 49.1% of patients. The multivariate logistic regression analysis showed an association ($p = 0.04$) between the staged urethral reconstruction and the incidence of urethral complications. The limitations of the study are its retrospective nature and the lack of control.

Despite the high incidence of postoperative complications and the possible need for revisions, TPR in the genetic male with PI using a RAFFF yields satisfactory aesthetic and functional results.

SEXUAL MEDICINE CALENDAR

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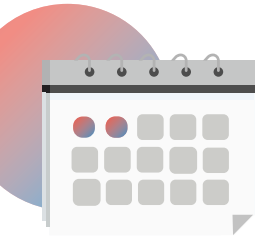

Check ESHRE – European society of human reproduction and embryology

SEPTEMBER

American Urological Association (AUA) Annual Meeting

10–13 SEP 2021

In-person meeting – Las Vegas, United States of America

https://www.aua2021.org/

OCTOBER

ESU-ESAU-ESGURS Masterclass on erectile restoration and Peyronie's disease

6–7 OCT 2021

Virtual meeting

https://esu-masterclasses.uroweb.org/masterclass/esu-esau-esgurs-masterclass-on-erectile-restoration-and-peyronies-disease/

12th EAU Section of Genito-Urinary Reconstructive Surgeons (ESGURS21) meeting

7–8 OCT 2021

Virtual meeting

https://esgurs.uroweb.org/the-meeting/

22nd Annual Fall Scientific Meeting SMSNA

21–24 OCT 2021

In-person meeting – Scottsdale, AZ, United States of America

https://www.smsna.org/annual2021/registration

NOVEMBER

US Professional Association for Transgender Health (USPATH) Scientific Symposium 2021

4–7 NOV 2021

Virtual meeting

https://www.wpath.org/education/upcoming-conferences

41th Congress of the Société Internationale d'Urologie (SIU)

10–14 NOV 2021

In-person meeting – Dubai, United Arab Emirates

https://www.siu-urology.org/congress-2021/

22nd World Meeting of the International Society of Sexual Medicine

19-21 NOVEMBER 2021

Virtual meeting

https://www.wmsm.org/

2022

Congress of the European Society of Sexual Medicine (ESSM)

17-19 FEB 2022

In-person meeting – Rotterdam, the Netherlands

https://www.essm-congress.org/