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HIGHLIGHTS FROM THE EDITION

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Contents

Welcome Address

The huge success of ISSM/ESSM 2018 Lisbon is just behind us and expectations for the upcoming ESSM 2019 meeting in Ljubljana, Slovenia, are gaining momentum. In this issue of ESSM TODAY we relive some of the highlights of the Lisbon meeting which point in the direction of what the future hot topics in Sexual Medicine will be.

Stem cell therapy or collagenase: which will be considered the next gold standard for the treatment of Peyronie's disease?

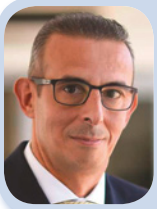
What will be the indications/ramifications of stem cell therapy in Sexual Medicine? And what about ESWT? How long before it becomes an established first line treatment for erectile dysfunction?

As always, many questions await us and answers abound and ESSM will do its best to present the facts based upon our vast, cumulative experience. In the meantime, this summer 2018, the sun shines upon the European Society of Sexual Medicine!

Ferdinando Fusco MD, PhD
Editor-in-Chief

Lisbon on the Wave of Sexual Medicine
A report from the Lisbon WMSM 2018

by Pedro Vendeira



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The 2018 World Meeting on Sexual Medicine (WMSM) was held in Portugal between February 28 and March 3, in the Lisbon Congress Center. Thematic diversity was the main "banner" of this meeting, which addressed oncossexuality, the most varied male and female sexual dysfunctions, infertility as a couple issue, and transsexuality among many other topics.

With about 1500 participants from 77 countries, this WMSM was one of the most participated ever in the field of Sexual Medicine, a feat that left the Local Committee, supported by the Portuguese Society of Andrology, Sexual Medicine and Reproduction, particularly pleased. Our Society worked hard to bring this meeting to Portugal, so it was a source of pride to see that the rooms were full and that the sessions were all heavily participated, a reflection of the interest that this meeting has aroused.

In a general analysis of the program, I would like to point out that it was quite eclectic, with the discussion of topics such as oncossexuality, emerging treatments for erectile dysfunction (including low intensity shock waves), or the challenges of penile transplantation and prosthetic surgery. I also would like to highlight the live surgery sessions that were held at Hospital de Santa Maria (Centro Hospitalar Lisboa Norte), and the debate on the psychological aspects associated with the pathologies under analysis.

Behind Sexual Dysfunctions

One of the concerns of the Scientific Committee, chaired by Prof. Maarten Albersen, representative of ESSM, and Dr. Wayne Hellstrom, representative of ISSM, was the commitment to the thematic diversity in order to extend the discussion to all professionals involved in the follow-up of patients with sexual disorders and fertility. That is, it was intended not only to address male dysfunctions but also female dysfunctions, as well as issues related to transgender individuals and the couple, focusing on the medical, surgical and psychological aspects involved.

The former president of ISSM also emphasized the importance of these meetings as a reliable scientific source of what is emerging again in the area, because there is still a lot of misinformation, especially on the Internet, where many people take advantage of those who do not have the knowledge to sell products without any scientific proof of its effectiveness. On the news discussed at WMSM 2018, the director of the Department of Urology at Tulane University School of Medicine in New Orleans, USA, highlighted the genetic therapeutics, regenerative medicine and the latest surgical devices and procedures.

Maarten Albersen, chair of the ESSM Scientific Committee, said that the dissemination of information is one of the priorities, as the support in this area varies greatly depending on the cultural and economic conditions of each country. In this sense, the also urologist in the University Hospital of Leuven, Belgium, defends that the pre-graduated formation in Sexual Medicine should be more in depth, because although this discipline is studied in medical schools around the world, this approach is done in a very fragmented way, which means that urologists only learn the issues related to male problems and gynecologists with women. With the ESSM educational programs, important steps have already been taken to provide a more multidisciplinary approach to sexual dysfunctions. While he considers that Sexual Medicine is already well on its way, Maarten Albersen acknowledges that there is still much more to be done. Research into female dysfunction is still very basic; patients who do not react to phosphodiesterase-5 inhibitors remain a challenge; and in the surgical field we are still very dependent on pumps, when we should have switched to electronic devices, batteries, etc.

Measurement of Sexual Responses

Prof. Pedro Nobre, president of the World Association for Sexual Health, moderated the round table "Hypersexuality: update 2018" and was speaker at the session "Measuring the sexual response in the lab" with the theme "Psychophysiological Measures". Assuming that hypersexuality is still a controversial issue, this professor and director of the PhD in Human Sexuality of the Faculty of Psychology and Educational Sciences of the University of Porto stated that in the so-called sexual compulsivity, people report a marked and an inability to control their sexual behaviours, but sometimes this concept is oversimplified as there are people who have a high and even above average sexual activity without this being synonymous with hypersexuality.

Local Organizing Committee

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Regarding the psychological evaluation of the sexual response, Pedro Nobre presented the work he has developed in the Laboratory of Research in Human Sexuality of the University of Porto, where he studies the answers (erection/vaginal vasocongestion) and psychological (excitement, pleasure and cognitive variables) during experiments in which people are exposed to sexual stimuli (usually films). In this context, he described the use of thermal cameras, which constitute a new technique of less invasive evaluation, and the role of emotions in the sexual responses. The sexual responses at the level of the genitals do not always correspond exactly to the self-report of excitement and pleasure. One of the factors that best explains these differences are the emotions and thoughts during sexual activity, which are related to the more subjective part of the sensation of excitement and pleasure. According to the researcher, these findings may be decisive for the future of the treatment of some sexual dysfunctions, since regardless of whether there is a greater or lesser genital sexual response, this does not invalidate that patients can improve the more subjective aspect, increasing their satisfaction and sexual well-being.

Prof. Luca Incrocci, ISSM's outgoing chairman and one of the decision-makers about the WMSM in Portugal, does not hide the satisfaction of the high participation in this congress of 2018 and the willingness to learn that the congressmen have demonstrated. Still, while admitting that a long way has gone, the deputy director of the Department of Radiation Oncology and Sexologist at the Erasmus Cancer Institute in Rotterdam, the Netherlands, believes that there is much more to improve, and it is necessary to advance to other areas of research, such as female dysfunctions or oncossexuality, betting on the development of new drugs capable of treating these problems in both sexes, as well as enhancing Sexual Medicine where it is most needed, that is, in the African continent and in many Asian regions.

It was in this sense that the ESSM Education Committee, chaired by Prof. Mikkel Fode, included in the program a pre-congress course and several workshops in a joint venture with ISSM. The course aimed to prepare participants for ECPS [EFS-ESSM Certified Psycho-Sexologist] and FECSM [Fellow of the European Committee for Sexual Medicine] exams.

Opening Ceremony

The main purpose of the workshops organized together with ISSM was to promote the exchange of experiences on the clinical practice of each one. Recalling that in many hospitals, sexual Medicine is not considered important, which means fighting on a daily basis for the recognition of this discipline and for the importance of treating these patients, the chairman of the ESSM Education Committee says that scientific meetings have three main purposes: to provide basic and advanced knowledge, to foster networking and to be a source of inspiration. Indeed it is always interesting to know what is emerging and to extend knowledge, because this may help us to get new ideas for further research.

On the latest advances in sexual medicine, this urologist at the University Hospital in Roskilde, Denmark, highlights the new treatment for premature ejaculation based on electrical stimulation of the pelvic floor and an investigation into the use of botulinum toxin to combat this problem, the possibility of performing penis implants only with local anesthesia and the new indications for the treatment of erectile dysfunction with low intensity shock waves.

Disruptive Thinking

The keynote lecturer for the WMSM 2018 was Tim Urban, co-founder, writer and illustrator of 'Wait But Why' website and author of the most watched TED Talk in 2016, about procrastination. Tim explained how thinking outside the paradigms can contribute to the future of Sexual Medicine. The motto of her conference at WMSM 2018 was a discussion of popular wisdom about Sexual Medicine. How is it possible to demystify wrong concepts which are culturally rooted? According to his thoughts, if we move into a world in which everyone is aware of their sexual health and this becomes a matter openly discussed, the change will unfold much more quickly. If the way of passing the message, whether oral or written, is fun and interesting, people pay more attention, they will seek to know more and share this message. Tim loves to take on complex subjects and treat them in a simple way. In his presentation at this WMSM he cleared the idea of the difference between the cooks and the chefs. It may seem simple, but it has a more complex thinking behind it. However, when one realizes the concept, that is, following recipes instead of playing with the ingredients,

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it is easier to perceive the difference. By recognizing that doctors are doing a really incredible and important job, though often it is not recognized as such, sexual health has a very significant impact on people's quality of life and is one of the most stigmatized issues. In 30 years we will look at this time as the "dark age" of Sexual Medicine. Tim added that these doctors are pioneers and are contributing to a paradigm shift in this area. That is why they should continue their good work, whether in clinical practice, research or the dissemination of these subjects, because they will certainly make a difference.

BOX 1

ISSM and ESSM: Desiderates of the New Presidents

The WMSM 2018 was also the occasion for the inauguration of the new ISSM presidents (Dr. Luiz Otávio Torres, from Brazil) and ESSM (Prof. Yacov Reisman, from the Netherlands). Stressing the importance of ISSM, which has about 2500 members from almost 90 countries, the Brazilian urologist reveals that education, the dissemination of sexuality and the strengthening of this society as the most respected scientific source in the world, are the three pillars in which it intends to base its mandate. "We aim to take sex education projects to places in the world that are less developed and do not have the opportunity, especially financial, to bet on training," he emphasizes. Yacov Reisman has chosen medical education and the demystification of sexuality as the main objectives of his mandate. "Contrary to the image transmitted by most media, gender, origin, beauty or physical vitality does not matter. Everyone has the right to sexuality, as enshrined in the World Health Organization, which is not limited to sexual activity, but also involves feelings of security and closeness to others."

BOX 2

Penile Transplantation Pioneer

The first surgeon to successfully perform a penile transplant in 2015 was Prof. Andre van der Merwe, an urologist at Tygerberg Hospital in South Africa, who shared this experience with the WMSM 2018 congressmen. "It took us about a year and a half to choose the transplant candidate and we were lucky enough to find a compatible donor, with good blood vessels. In addition, the receptor was so healthy that, at least initially, it had no side effects of immunosuppression". As for the specificities of the surgery, the speaker listed two major challenges: to achieve a good blood supply, taking into account that the transplanted vessels can not be used because they gain fibrosis, and to connect to the bladder without leaving the patient incontinent. Counting to soon begin teaching the procedure to other colleagues, including Portuguese, Andre van der Merwe pointed out that many people are waiting for a penile transplant, especially transgender individuals. "About 56% of these people are on the waiting list because, despite the adverse effects of immunosuppression, they prefer to have a penis. However, a way of overcoming the discrepancy between the size of the penis and the clitoris is still under study. "

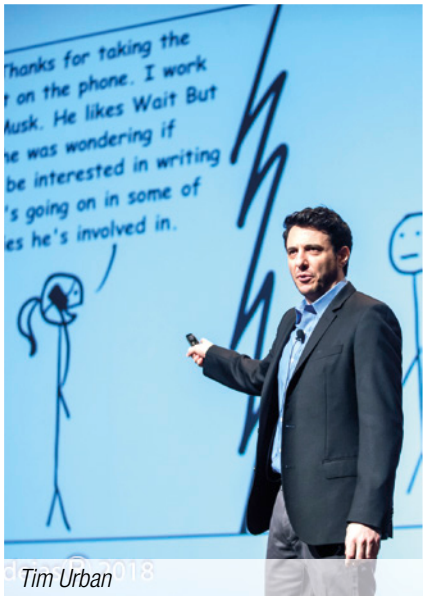
BOX 3

National Excellence

During the WMSM 2018, the ECPS (EFS-ESSM Certified Psycho-Sexologist) and FECSM [Fellow of the European Committee for Sexual Medicine] exams were also carried out, in which respectively 2 and 14 Portuguese were approved, an evident demonstration of how Portuguese Sexual Medicine is evolving and attracting young scientists to the field.

Pedro Nobre

Andre van der Merwe



Tim Urban

Stem cell therapy in Andrology – are we ready for prime time?

by Dorota J. Hawksworth and Trinity J. Bivalacqua

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Stem cell therapy has been in use for the last two decades and is currently utilized to treat many medical conditions including malignant, hematologic, cardiovascular, neurologic and immunologic-based diseases. Recently, great attention has been directed to this form of therapy within the field of Sexual Medicine, as increasing number of basic science studies demonstrate promise in treating erectile dysfunction (ED), Peyronie's disease (PD) and infertility. [1-3]

Stem cells (SCs) are unspecialized precursor cells capable of self-renewal and differentiation into various cell types, depending on the stimuli they receive. Based on their origin, they are further sub-classified into embryonic stem cells (ESCs) and adult stem cells (ASCs). ESCs, as their name implies, are derived from the embryonic, inner cell mass of the blastocyst, while ASCs are derived from native tissues of a developed individual. SCs are further divided based on their differential potential into totipotent, pluripotent and multipotent. While a fertilized egg is considered totipotent, as it can differentiate into any cell line, ESCs are pluripotent and can differentiate into any cell type with the exception of the fertilized egg. Lastly, ASCs are multipotent and can differentiate into organ-specific cell types. In the field of Sexual Medicine, ASCs have been investigated most in pre-clinical settings and in humans with sexual dysfunction.

Various types of ASCs have been discovered, with mesenchymal stem cells (MSCs) constituting the largest group. Bone marrow stem cells (BMSCs) are a subgroup of the MSCs that were discovered early on and have been studied thoroughly as treatment option for degenerative and inflammatory diseases. [4] The discovery of adipose-derived stem cells (ADSCs) followed at the turn of the last century and since then ADSCs have been determined to be virtually identical to the BMSCs. [5] Currently, the ease and safety involving adipose tissue abundance and isolation as well as much higher yield of cells from ADSCs than BMSCs, make the former an overall much more attractive form of ASCs.

Although ESCs have a much superior differentiation potential than the ASCs, ethical concerns and regulatory constraints regarding their use hamper their research application. To date, there is only a handful of published studies evaluating use of ESCs, with only one of them performed in a cavernosal nerve injury rat model. In the study, Bochinski et al. demonstrated significant beneficial effects of the ESC therapy, with recovery of erectile function and improved quality of the nerve fibers. [6] Other studies focused mainly on male infertility, and demonstrated that ESCs were able to differentiate into male germ cells in vitro and subsequently, those ESC-derived germ cells were able to generate offspring mice. [7]

ASC research is advancing at a much faster rate because of the lack of regulatory control and ease of isolation. To date, pre-clinical animal studies in multiple ED models of disease utilizing ASCs-based therapies have been performed and established their safety, efficacy and mechanisms of action. The vast majority of the studies are focused on either acute (neurogenic) or chronic (diabetes, atherosclerosis, aging and hypogonadism-related) etiologies of ED. All of the rat and rabbit models utilized so far, consistently demonstrated improved erectile function following SC therapy.

Additionally, the studies involving animal models of non-obstructive azoospermia also demonstrated significant findings, as they established the ability of the murine BMSCs to differentiate into male germ cells, Sertoli and Leydig cells. [7, 8] Another approach to the SC use is spermatogonial stem cell (SSC) transplantation. This technique was first described in 1994 when samples of testicular cells from fertile mice were transplanted into infertile mice and resulted in fertility restoration. [9] Studies show that following SSC transfer into the recipient animal, SSCs migrate to the basement membrane of the seminiferous tubules, self-renew and differentiate to establish spermatogenesis. [10] At present, however, although this use of SCs seems very promising, it remains experimental and has not been attempted in humans. [11]

More recently, animal studies in the field of Sexual Medicine are also focusing on the anti-fibrotic properties of ADSCs and their role in attenuation of symptoms related to Peyronie's disease. So far, scientists found that several molecular signaling pathways are either attenuated or activated by ADSC therapy and ultimately result in an increased expression of matrix metalloproteinases (MMPs) responsible for collagen degradation, and ultimately suppressed collagen contraction. [2, 12, 13]

Now, as the animal models have demonstrated very promising results, over the last few years, researchers have been shifting their focus onto

human clinical trials and currently data on four such trials involving ASC therapy for ED have been published. All four of them were non-randomized, single arm studies and accrued small numbers of patients. As each of the studies evaluated SCs from a different source including umbilical blood, placenta, adipose tissue and bone marrow, it is difficult to draw strong supportive evidence for this therapy as a whole. On a positive note, neither of the studies had any reported adverse outcomes and all demonstrated at least mild improvements in the ED measures. [14-17] However, we need to take these early trial results with much caution, as they are not randomized and only show safety. Proper, well-designed randomized trials are necessary.

As demonstrated in this communication, the stem cell research is rapidly advancing, and multiple animal and now newly emerging human data support its use, it is developing into a very promising therapeutic option for ED, PD and even severe forms of infertility. The therapeutic application of SCc however, is still facing few, albeit very valid challenges before it becomes fully ready for prime time. Besides ethical, regulatory and financial constraints, issues concerning the best source of SCs, their uniform method of application, dosing, as well as long-term efficacy, oncogenic safety in post-prostatectomy patients and overall safety must still be addressed.

Until these issues are fully evaluated and established, for now, professional position statements such the one recently released by our own, the Sexual Medicine Society of North America (SMSNA), should be strongly respected and enforced. As such, stem cell use *"should be conducted under research protocols in compliance with Institutional Board approval"* and *"patients considering such therapies should be fully informed and consented regarding the potential benefits and risks"*.

REFERENCES

1. Matz, E.L., et al., **Stem cell therapy for erectile dwysfunction**. Sex Med Rev, 2018.
2. Sangkum, P., **Research highlights on stem cell therapy for the treatment of Peyronie's disease.** Transl Androl Urol, 2016. 5(3): p. 363-5.
3. Vij, S.C., E. Sabanegh, Jr., and A. Agarwal, **Biological therapy for non-obstructive azoospermia.** Expert Opin Biol Ther, 2018. 18(1): p. 19-23.
4. Phinney, D.G. and D.J. Prockop, **Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair – current views.** Stem Cells, 2007. 25(11): p. 2896-902.
5. Strem, B.M., et al., **Multipotential differentiation of adipose tissue-derived stem cells.** Keio J Med, 2005. 54(3): p. 132-41.
6. Bochinski, D., et al., **The effect of neural embryonic stem cell therapy in a rat model of cavernosal nerve injury.** BJU Int, 2004. 94(6): p. 904-9.
7. Nayernia, K., et al., **In vitro-differentiated embryonic stem cells give rise to male gametes that can generate offspring mice.** Dev Cell, 2006. 11(1): p. 125-32.
8. Lue, Y., et al., **Fate of bone marrow stem cells transplanted into the testis: potential implication for men with testicular failure.** Am J Pathol, 2007. 170(3): p. 899-908.
9. Brinster, R.L. and J.W. Zimmermann, **Spermatogenesis following male germ-cell transplantation.** Proc Natl Acad Sci U S A, 1994. 91(24): p. 11298-302.
10. Ogawa, T., et al., **Transplantation of testis germinal cells into mouse seminiferous tubules.** Int J Dev Biol, 1997. 41(1): p. 111-22.
11. Giudice, M.G., et al., **Update on fertility restoration from prepubertal spermatogonial stem cells: How far are we from clinical practice?** Stem Cell Res, 2017. 21: p. 171-177.
12. Castiglione, F., et al., **Intratunical injection of human adipose tissue-derived stem cells prevents fibrosis and is associated with improved erectile function in a rat model of Peyronie's disease.** Eur Urol, 2013. 63(3): p. 551-60.
13. Jiang, H., et al., **Inhibition of penile tunica albuginea myofibroblasts activity by adipose-derived stem cells.** Exp Ther Med, 2017. 14(5): p. 5149-5156.
14. Bahk, J.Y., et al., **Treatment of diabetic impotence with umbilical cord blood stem cell intracavernosal transplant: preliminary report of 7 cases.** Exp Clin Transplant, 2010. 8(2): p. 150-60.
15. Haahr, M.K., et al., **Safety and potential effect of a single intracavernous injection of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy: an open-label phase I clinical trial.** EBio Medicine, 2016. 5: p. 204-10.
16. Levy, J.A., et al., **Determining the feasibility of managing erectile dysfunction in humans with placental-derived stem cells.** J Am Osteopath Assoc, 2016. 116(1): p. e1-5.
17. Yiou, R., et al., **Safety of intracavernous bone marrow-mononuclear cells for postradical prostatectomy erectile dysfunction: an open dose-escalation pilot study.** eur urol, 2016. 69(6): p. 988-91.
18. Sexual Medicine Society of North America. **Position statement: ED restorative (regenerative) therapies (shock waves, autologous platelet rich plasma, and stem cells).** 2018.

The EFS & ESSM Certified Psycho-Sexologist (ECPS) exam: The 3rd successful edition

Chiara Simonelli interviews Evie Kirana

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C.S.: The EFS & ESSM Certified Psycho-Sexologist (ECPS) exam has successfully arrived at the 3rd edition, which has been held in the beautiful frame of Lisbon on 28th February 2018. This challenging adventure started in 2014 in Istanbul. Where does the idea come from?

E.K.: The ESSM and EFS have been collaborating since 2013 to promote the highest standards of healthcare in the field of Sexology and Sexual Medicine. This was an initiative of the two presidents of EFS and ESSM at that time (Chiara Simonelli and Hartmut Porst – editor's note). As a result of this collaboration, a certification procedure has been initiated to distinguish excellence amongst individual psych-sexologists from around the world.

C.S.: As said, we are now at the 3rd ECPS exam (1st in Istanbul in 2014 and the 2nd in Madrid in 2016). How was this edition and how many ECPSs are there now in the world?

E.K.: The European Psycho-sexology Accreditation (E.P.S.A.) committee has developed a long-term plan to protect and to enhance the role of psycho-sexologists in Europe. Within this context, the eligibility criteria for someone to apply are of high standards. Today, and after 3 examination periods, we have about 100 people who have obtained the EFS and ESSM psycho-sexologist accreditation certificate. Please note that the work of this committee applies to psycho-sexologists, so it refers to the field of sexology relevant to psychologists and/or psychiatrists.

C.S.: The success of such a certification costs of many efforts. I was wondering about the people working behind. Who is the core of the ECPS organization?

E.K.: As with most such activities, there is a group of people working. We have the full members, the honorary advisors and the associate members. Full members of the E.P.S.A. have the duty to design, organize and implement tasks for the accreditation of psycho-sexologists and relevant educational courses. Today, the full members are:

- (Chair) Evie Kirana, Psychologist (Greece)
- Janico Georgiadis, Neuroscientist (The Netherlands)
- Tilmann Krueger, Psychiatrist (Germany)
- Lior Lowenstein, Gynecologist (Israel)
- Yacov Reisman, Urologist (The Netherlands)
- Francesca Tripodi, Psychologist (Italy)
- Remziye Kunelaki, Psychologist (UK)
- Xanti Ntoni-Fynbo, Psychologist (Denmark)

Honorary advisors are prominent scientists of international repute and high distinction that serve in advisory capacity to the E.P.S.A. committee. Their role is to provide advice to the committee on scientific and executive issues that come within their experience and expertise.

1. Prof. Pedro Nobre (Portugal)
2. Prof. Chiara Simonelli (Italy)
3. Prof. Alain Giami (France)
4. Prof. Erick Janssen (Belgium)
5. Prof. Kevan Wylie (UK)
6. Prof. Uwe Hartmann (Germany)
7. Prof. Astrid Højgaard (Denmark)
8. Prof. Peter Weiss (Czech Republic)
9. Prof. Rafi Heruti (Israel)
10. Prof. Anita Clayton (USA)
11. Prof. Jim Pfaus (Canada)

An Associate Member is someone that contributes to the objectives of E.P.S.A. by participating in specific projects that aim to facilitate the role of psycho-sexologists in Europe. The Associate Member could be an EFS/ESSM certified psycho-sexologist (ECPS) that has demonstrated special interest in EFS/ESSM educational activities or has had an active role within national or international societies and would like to be involved in the work of the E.P.S.A. Associate members are assigned specific tasks under the supervision of full members. Such tasks may involve, for example, mapping of educational events relevant to sexology or the dissemination of information relative to the exam etc.

So, if somebody would like to become an associate member please let us know!

C.S.: The joint EFS and ESSM adventure is not only represented by the exam. Which other projects have been shared so far?

E.K.: In an unofficial way, one can very often see scientists participating at activities of both societies. Whether these are educational or research activities. This is reasonable as sexual health is a multidisciplinary field, and it is this that makes it so unique. In terms of formal collaboration, the two societies had implemented a common congress in the past. Today, the ECPS is the field of collaboration, and I personally, would hope for more common projects in the future. Not only joint congresses, but also joint educational activities and research activities. In my perspective, by joining the EFS and ESSM human and capital resources, we would not only manage our resources more effectively, but we would also develop activities that enhance sexual health through a bio-psychosocial perspective.

Still round the corner there may wait, a new road or a secret gate: Stem cell therapy for Peyronie's disease

by Fabio Castiglione and Asif Muneer

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Stem Cell therapy for Fibrosis

Fibrosis is defined by an excessive accumulation of extracellular connective tissue proteins (extracellular matrix (ECM)) such as collagen, elastin and fibronectin. Typically, ECM aggregation is an essential and reversible phase of the wound healing process (1). It can however evolve into a gradually permanent fibrotic reaction if the tissue injury is grave, repetitive, or in case the wound-healing process itself becomes deregulated. Fibrosis represents the conclusive, typical pathological consequence of many chronic inflammatory disorders and can lead to a progressive loss of organ function (2).

Adult mesenchymal stem cells (MSCs) are classified as multipotent stem cells which differentiate into several types of mesenchymal cells. Until recently this property had only been studied for its direct medical implications and therapeutic uses. However, MSCs release a wide spectrum of regulatory and trophic factors (growth factors, cytokines and chemokines). This suggests a paracrine effect as "site-regulated drugstores" in vivo and can have an effect on tissue even if they do not engraft or differentiate (3). In the last decades, researchers have tried applying SCs by exploiting their immune-regulatory properties to several therapeutic scenarios. A few examples include graft-versus-host disease (GVHD) in bone marrow transplantation, multiple sclerosis, brain and spinal cord injury, arthritis, myocardial infarction and Crohn's disease (4).

More importantly, over the last few decades, there is an accumulation of evidence that SCs play a major role in normal wound healing. They accelerate wound contraction, process and increase the quality of the tissue, counteract healing anomalies and reduce the amount of ECM produced. The latter contributes to a better cosmetic result of the scar tissue (5).

Supported by this evidence, it is unsurprising that several studies were performed evaluating the efficacy of SCs in treating fibrotic disorders with positive results especially for Lung and liver fibrosis (6,7).

The anti-fibrotic properties of SCs are not yet properly understood and are a topic of intensive research. A growing body of evidence, however, suggests SCs act via immunomodulation, ROS neutralization and angiogenesis (8–10) (fig.1).

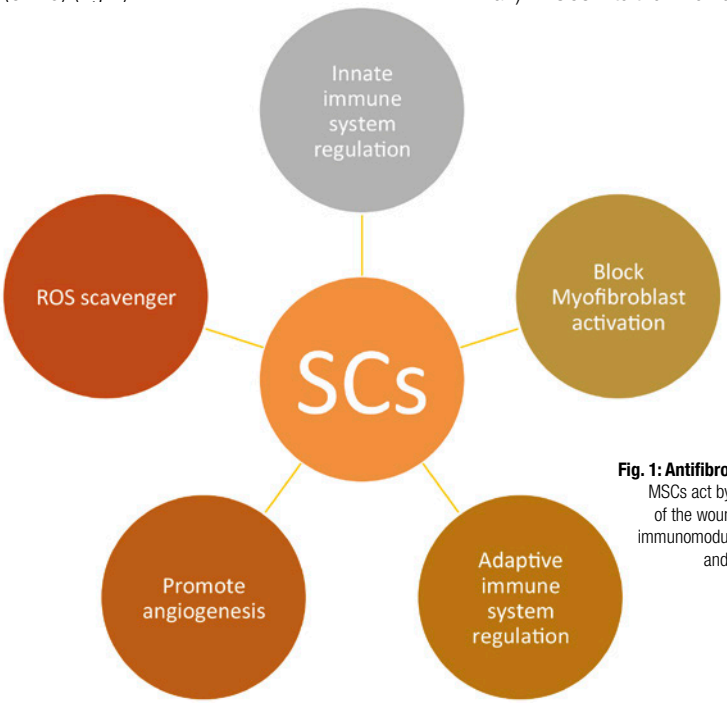


Fig. 1: Antifibrotic properties of MSCs
MSCs act by modulating all the steps of the wound healing exploiting their immunomodulation, ROS neutralization and angiogenesis properties.

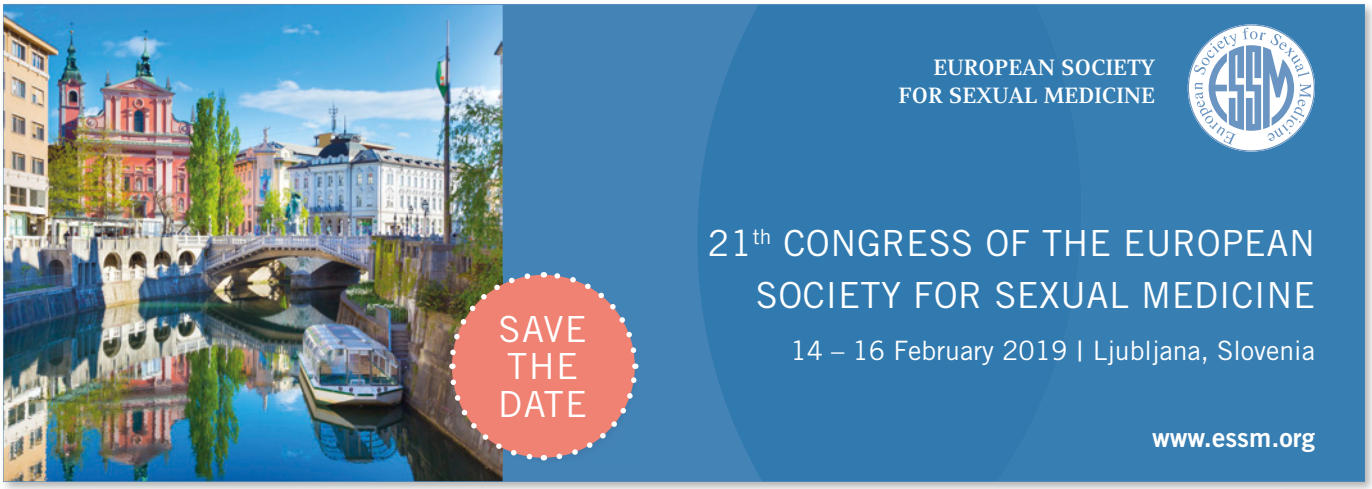
Stem cell therapy for PD – what the evidences really says…

Peyronie's disease (PD) represents localized connective penile tissue disorders characterized by changes in collagen composition of the tunica albuginea (TA) (11). The consequences of these conditions can enormously impair the patient's sexual quality of life by causing curvature of the penis, impairment of erectile function and erection-related pain (11). Commonly, PD is classified into an acute (or inflammatory) phase and a chronic (or stable) phase. During the chronic phase, since the inflammatory process has settled, pain is absent and the curvature and TA fibrosis are stable. In the last 2 decades, several antifibrotic drugs have been tested as treatment for PD. Unfortunately, except for collagenase, none of these drugs exhibit sufficient therapeutic benefit (12).

To date 3 studies had tested the mesenchymal stem cells local injection as therapy for PD (13–15) in animals.

Castiglione et al. (13) were the first to show the efficacy of adipose derived stem cells (ADSCs) in PD. They injected xenogeneic (human) ADSCs into the TA of rats with experimen-

Still round the corner there may wait, a new road or a secret gate: Stem cell therapy for Peyronie's disease



tally induced PD. Five weeks after the ADSC local injection into the site of inflammation, the rats had less elastosis and fibrosis of the TA compared to the untreated rats and, surprisingly, no erectile dysfunction. The authors showed that the total content of elastin decreased by 47.7% in the treated rats compared with untreated rats. Also, the collagen III concentration was reduced by 69.9% after ADSC injection. At IM analysis of Collagen III and elastin content of the TA, the author also found corporal fibrosis near the TA plaque. This phenomenon was completely prevented by the hADSCs injection (13).

Despite the first evidence of the benefit of SCs in treating PD, most patients present to their clinician with chronic PD, and thus these results cannot be directly translated into a clinical application.

Two preclinical studies from the group of Hellstrom (14,15) have evaluated the efficacy of allogeneic ADSCs and genetically modified allogeneic ADSCs expressing human InterferonA-2b for the prevention and treatment of TA fibrotic plaque tissue. In the first study (14), the allogenic-ADSC treated groups received tunica albuginea injections with 0.5 million rat ADSCs immediately after (early phase) or 1 month later (late phase) the TGF-β1 injection. Six weeks after TGF-b 1 injection, in both prevention and treatment groups, injection of both types of ADSCs resulted in significantly lower tunica albuginea fibrosis and in a better erectile function compared with rats treated only with TGF-β1 (14).

The authors also investigated the possible antifibrotic mechanism. Local injection of ADSC seems to decrease the expression of tissue inhibitors of metalloproteinases (TIMPs), and promoting the production and activity of MMPs. Despite this being a landmark study, highlighting the possibility that ADSC can be used to effectively treat and counteract the established fibrosis with which patients usually present themselves, there are some limitations. The main issue is the method used in the evaluation of fibrosis. The authors only used a qualitative analysis MT stained section of the penis without performing any quantitative analysis of these images (14).

In the latter study (15), Gokce et al. compared the efficacy ADSCs expressing human interferon a -2b and normal allogeneic ADSC in the prevention and treatment of PD using a similar design of their previous study. The data of this study showed that both types of cells are efficient in preventing and treating Peyronie-like changes (15).

Are we ready for the clinical trial? No!!!

The rapidly expanding preclinical evidence in SC medicine providing a potential treatment for several fibrotic diseases. All the available antifibrotic treatment act against one step of the redundant fibrotic pathway. Conversely, SCs, acting against several steps, are potentially superior to the current treatments (16).

Based on the available data, it seems that SCs treatment can be applied to PD. However, the research in this field is still poor and with several limitations that may jeopardize the clinical application. The large part of the studies exploring the efficacy of SCs PD showed that SCs are able to prevent the insurgence of TA fibrosis. On the other hands there are only few evidences that the SCs treatment is efficacious in reverse fibrosis when it is established. This aspect is of outmost importance for the translation point of view owing to the large part of patients is already affected by chronic PD.

In addition, it is worth remembering that there are several issues linked with SC treatment that still has to be clarified. The dispute of allogeneic versus autologous versus xenogenic source must to be investigated. Despite ADSC representing the most common type of SC used. AD-Stromal vascular fraction seems to be a better choice for oncological issues. Timing of SC injection represents another especially because it seems that SCs show an antifibrotic phenotype only when they are in an inflammatory environment. The dosage of SCs in preclinical study is arbitrary and it is not yet clear if the number of SC injected can influence the phenotype of the SCs.

Despite of the research on SCs and penile fibrosis is at an embryonic state and plenty of limits. We think that with more translation studies valuating SCs efficacy, clinical trials for the treatment of penile fibrosis could be anticipated in the near future.

Still round the corner there may wait, a new road or a secret gate: Stem cell therapy for Peyronie's disease

References

1. Wynn T.A., **Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases.** J Clin Invest [Internet]. 2007/03/03. 2007;117(3):524-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17332879
2. Wynn T.A., **Cellular and molecular mechanisms of fibrosis.** J Pathol. 2007/12/29. 2008;214(2):199-210.
3. Caplan A.I., Correa D., **The MSC: an injury drugstore.** Cell Stem Cell [Internet]. 2011/07/06. 2011;9(1):11-5. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21726829
4. Bora P., Majumdar A.S., **Adipose tissue-derived stromal vascular fraction in regenerative medicine: a brief review on biology and translation.** Stem Cell Res Ther. 2017/06/18. 2017;8(1):145.
5. Jackson W.M., Nesti L.J., Tuan R.S., **Mesenchymal stem cell therapy for attenuation of scar formation during wound healing.** Stem Cell Res Ther. 2012/06/07. 2012;3(3):20.
6. Gomperts B.N., **Strieter RM. Stem cells and chronic lung disease.** Annu Rev Med. 2006/08/05. 2007;58:285-98.
7. Chang Y.J., Liu J.W., Lin P.C., Sun L.Y., Peng C.W., Luo G.H., et al., **Mesenchymal stem cells facilitate recovery from chemically induced liver damage and decrease liver fibrosis.** Life Sci. 2009/08/19. 2009;85(13–14):517–25.
8. Singer N.G., Caplan A.I., **Mesenchymal stem cells: mechanisms of inflammation.** Annu Rev Pathol. 2010/11/16. 2011;6:457-78.
9. Meirelles L. da S., Fontes A.M., Covas D.T., Caplan A.I., **Mechanisms involved in the therapeutic properties of mesenchymal stem cells.** Cytokine Growth Factor Rev. 2009/11/21. 2009;20(5–6):419–27.
10. Sorrell J.M., Caplan A.I., **Topical delivery of mesenchymal stem cells and their function in wounds.** Stem Cell Res Ther. 2010/09/25. 2010;1(4):30.
11. Garaffa G., Trost L.W., Serefoglu E.C., Ralph D., Hellstrom W.J., **Understanding the course of Peyronie's disease.** Int J Clin Pr [Internet]. 2013/07/23. 2013;67(8):781-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23869679
12. Gabrielson A.T., Spitz J.T., Hellstrom W.J., **Collagenase Clostridium Histolyticum in the treatment of urologic disease: Current and future impact.** Sex Med Rev. 2017/04/30. 2017
13. Castiglione F., Hedlund P., Van der Aa F., Bivalacqua T.J., Rigatti P., Van Poppel H., et al., **Intratunical injection of human adipose tissue-derived stem cells prevents fibrosis and is associated with improved erectile function in a rat model of Peyronie's disease.** Eur Urol [Internet]. 2012/10/09. 2013;63(3):551-60. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23040209
14. Gokce A., Abd Elmageed Z.Y., Lasker G.F., Bouljihad M., Kim H., Trost L.W., et al., **Adipose tissue-derived stem cell therapy for prevention and treatment of erectile dysfunction in a rat model of Peyronie's disease.** Andrology. 2014/02/28. 2014;2(2):244-51.
15. Gokce A., Abd Elmageed Z.Y., Lasker G.F., Bouljihad M., Braun S.E, Kim H., et al. **Intratunical injection of genetically modified adipose tissue-derived stem cells with human interferon alpha-2b for treatment of erectile dysfunction in a rat model of tunica albugineal fibrosis.** J Sex Med. 2015/06/11. 2015;12(7):1533-44.
16. Caplan A.I., Dennis J.E., **Mesenchymal stem cells as trophic mediators.** J Cell Biochem. 2006/04/19. 2006;98(5):1076-84.

See application form on page 22.

Can collagenase make it right?

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About Peyronie's disease

Peyronie´s disease (PD) is condition that results from fibrotic plaque formation of the tunica albuginea, and it can result in a number of penile deformities such as cuvature, shortening, narrowing, hour-glass deformity and/or hinge deffect. PD usually affects men in their 50s and the estimated incidence varies from 3% to 9% [1]. The etilogy of PD remains unknown, but the most accepted hyphotesis is that vascular microtrauma during sexual intercourse releases an uncontrolled inflammatory reaction in genetically susceptible men (2).

The most common presentation of PD is in two well divided phases: acute and chronic. During the acute inflammatory phase the plaque begins to form and the deformities become apparent. Men tipically present pain during this phase. In the chronic phase the pain usually disappears and the curvature stabilizes. The plaque begins to harden and, although described, the curvature rarely resolves spontaneously [3]. Depending on the severity of the curvature, men with PD may find penetrative sexual intercourse difficult or impossible, causing psychological, emotional and relation problems [4].

Although surgical correction of the curvature remains the gold-standard treatment for PD, many conservative treatments have been postulated, including extracorporeal shockwave therapy, iontophoresis and intralesional, topical and oral agents. None of this treatments have demonstrated its efficacy and safety in large, well designed clinical trials [5]. Surgical correction is indicated in men with estable disease unable to have penetrative sexual intercourse. Although the results of surgery in centers with experience correcting the curvature or penile deformity is usually excellent, the different procedures have collateral effects that may be undesirable (penile shortening, erectile dysfunction) [6].

The development of the collagenase of the Clostridium Histolyticum

Collagenase of the Clostridium histolyticum (CCH; Xiapex®, Swedish Orphan Biovitrum AB, Stockhom, Sweden; Xiaflex®, Endo Pharmaceuticals, Malvern, PA, USA) is the first treatment approved by the US Food and Drug Administration and the European Medicines Agency for the non-surgical management of PD. Collegenases are protease enzymes that under normal physiologic conditions hydrolyze collagen fibers. CCH contains a misture of class I and II collagenases in a defined ratio. Both classes act on different parts of the collagen molecule, allowing them to work synergistically. CCH has been found to work selectively on collagen types I and III, which are the predominant forms in PD, and spares collagen type IV, the main one found in arteries, veins and nerves. This selective nature of CCH lessens the chance of adjacent structures being affected [7].

The first in vitro experience about using CCH to treat PD was published in 1982, using Peyronie's plaques of three men in addition to pericardial and corporal tissue. Histologic examination of the tissues found that CCH reduced the plaques and spared the arteries, nerves and elastic tissues, although there was some disruption to the collagen found in small venules [8].

Some years later, in 1985, Gelbard et al. conducted the first pilot study of intralesional CCH in 31 men with PD, who received an increasing dose of CCH due to the lack of adverse effects noted with the first and lower doses. They found an objective improvement in penile curvature in 20 men after completion of treatment. Of those men whose primary complaint was pain, 13 of 14 described resolution of that symptom after injection with CCH. A small corporal rupture managed conservatively was noted in one patient, but no other adverse effects were reported [9].

Gelbard et al. also conducted a further phase I prospective, randomized, placebo-controlled clinical trial published in 1993. They randomized 49 men to the treatment (CCH) and control (saline injection) groups. They stratified the participants in three categories according to the severity of the disease: category 1, with patients with a curvature ≤30º and/or palpable plaque less than 2 cm; category 2, with patients dispalying a curvature 30º to 60º and/or plaque size of 2 to 4 cm; and category 3, with patients >60º and/or plaque greater than 4 cm. The protocol consisted in one injection of a variable quantity of CCH or saline solution depending on the severity of the disease. A significant improvement in the angle of penile curvature and a reduction of the plaque size was found in the treatment group, with no adverse effects noted after 3-month follow-up [10].

Further evaluation of the safety and efficacy of CCH was investigated in a phase IIb double-blinded, randomized, controlled trial with 147 participants. They were randomized into four groups to receive CCH or saline placebo (3:1) with or without investigator penile modeling (1:1). Each cycle of treatment consisted of two injections (CCH or placebo) 24 to 72 hours apart, with each patient receiving three cycles separated by 6 weeks. Investigator modeling was performed 24 to 72 hours after the second injection of each treatment cycle. The mean decrease in curvature with CCH was 29% compared to 11% with placebo (p=0.001). A further decrease (32.4%) in curvature was found in men who underwent modeling after CCH injection compared with worsening of 2.5% in the control group (p<0.001). No serious adverse events were noted [11].

Taking into account all these accumulated data, it was not until 2013 when "The Maximal Peyronie's Reduction Efficacy and Safety Studies I and II" (IMPRESS I and II) paper was published. These are two identically designed, large, randomized, controlled, phase III clinical trials investigating intralesional CCH injection in men with PD, recruiting a total of 832 participants. Patients with dorsal, lateral or dorsolateral penile curvature of 30º to 90º were included, and those with ventral curvature and calcified plaque were excluded. Men were stratified into a group with 30º to 60 curvature (77.3%) and a group with 60º to 90º curvature (22.7%), and then randomized to an intervention or a control group (2:1). The intervention group received up to four cycles that were 6 weeks apart, and for each cycle, participants received two intralesional CCH (0.58 mg) injections separated by 24 to 72 hours, and the returned for investigator modeling after another 24 to 72 hours. The control group was injected with tris 10 mmol/L and sucrose 60 mmol/l as placebo. There was a mean decrease in curvature of 17º (34%) in the intervention groups compared with 9º (18%) in the control groups ($p<0.0001$) [12].

Another phase III open-label clinical trial conducted by Levine et al. recruited 347 participants and used the same primary end points as the IMPRESS trials, which found a 34% (-18.3º) mean decrease in curvature. They also performed a subgroup analysis that showed a 33% improvement in men from the 30º-60º group, and a 37% improvement in men from the 60º– 90º group [13].

Combination theraphy, new indications and modified protocols

Since the official approval of CCH, and in parallel to the growing number of centers that incorporated it as a valid treatment for PD, some publications have suggested modifications of the original protocol or inclusion criteria.

Thus, Ralph et al published in 2017 the results of a prospective study involving 53 patients with PD and treated with CCH using a new protocol. Under a penile block of 10 mL plain lignocaine 1%, a total of three intralesional injections of CCH (0.9 mg) were given at 4-weekly intervals. The whole vial was used and injected in multiple positions at the apex of the curvature in the flaccid penis. In between injections, patients used a combination of home modelling, stretching, and a vacuum device on a daily basis, but no investigator modelling was performed. 51 of the 53 patients had an improvement in the angle of curvature by a mean (range) of 17.36º (0º-40º) or 31.4% (0%-57%) from baseline after three CCH injections. There was an improvement in each of the IIEF questionnaire domains, all three PDQ domains and the GAPD. They concluded that the results of using just three CCH injections according to this modified protocol are comparable to those of the clinical trials that used eight CCH injections, reducing this way the duration and the cost of the treatment [14].

The usefulness the the CCH therapy in combination with other treatments for PD has also been explored. Previous reports have suggested a role for penile traction therapy (PTT) as monotherapy for PD, with improvements noted in stretched penile lenght, penile curvature (in the acute phase), and patient satisfaction. Ziegelmann et al. hypothesized that PTT in combination with CCH would result in greater improvements in penile curvature and lenght relative to CCH alone. They recruited a total of 51 patients who underwent a similar protocol to the described in the IMPRESS I and II, including manual modelling and stretching. The mean (SD) improvement in penile curvature was 20.9º (17.3º, $p<0.0001$), with no significant difference indentified in the degree of curve improvement based on frequency or duration of PTT. Based on their results, the clinical use of concurrent PTT during CCH therapy appears limited [15]. Nevertheless, Ralph et al. performed a recent study evaluating the efficacy and safety of CCH plus vacuum-pump therapy with and without penile modeling. They recluted 30 patients that were offered a standard CCH treatment of a maximun of 4 cycles 6-week apart with 2 injections for each cycle. They found no significant difference in the curvature improvement between both groups, but the results seem to be slightly better than the previously reported in similar studies without using the vacuum therapy (mean change from baseline -23.7º [SD=10.9] for CCH+vacuum+modeling and -23.3º [SD=7.2] for CCH+vacuum; between-group difference=0.3º, 95% CI = -7.3 to 6.6) [16].

In order to furtherly optimize the treatment and make a good selection of the candidates to receive this therapy, some groups are currently studying the importance of different factors of the disease to help to predict it success. It has

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been postulated that calcification of the plaque, primary curve direction, and degrees composite curvature may play an important role in predicting the response to CCH therapy. But to date, only moderated (shadowing) or severe (>1 cm) calcification of the plaque has been demostrated to be a predictive factor for poor response. This fact can make mandatory the performance of complementary evaluation of the plaque (ultrasound) before offering this treatment [17].

However, the inclusion criteria of the patients with PD to be treated with CCH may be wider in the future. Although all the previous trials exclude patients with an active disease, in a 2017 paper Nguyen et al describe their experience treating men with an active PD. From a total series of 162 patients, 36 were considered to be in an active phase. They found no significant difference in final change in curvature between the acute and stable phases of PD (16.7° vs 15.6°; p=0.654), and there was also no statistically significant difference in frequency of treatment-related adverse events between the acute phase (4 patients, 11%) and the stable phase (12 patients, 10%; p=0.778). When treating PD in active phase, it could be possible to improve the results of CCH therapy because it is supposed that the penile deformities present should be milder. But we should be cautious about the long term results of the treatment, as long as the evolution of the disease may be unclear beyond the end of the injections [18].

CCH represents the first non-invasive treatment with demonstrated efficacy, but till date is a novel and still limited treatment to some selected patient suffering PD. Althought it may not avoid surgery in every patient, we think that it could have a paper improving the conditions patients face the procedure, as long operating a milder curvatures has less potential complications. Given the fact that is a expensive treatment, it is of major importance to further describe the predictor factors for a good response, and design studies to evaluate its cost-efficacy including the potential known complications of the different surgical procedures. It is also interesting to study its potencial indication in patients with active disease, given the fact that this could avoid the development of a more severe disease.

References

1. Pryor J.P., Ralph D.J., **Clinical presentations of Peyronie's disease.** Int J Impot Res 2002;14:414-417.
2. Herati A.S., Pastuszak A.W., **The genetic basis of Peyronie's disease: a review.** Sex Med Rev 2016;4:85-94.
3. Kadioglu A., Tefekli A., Erol B., et al., **A retrospective review of 307 men with Peyronie's disease; results of a large survey.** BJU Int 2001;88:727-730.
4. Goldstein I., Hartzell R., Shabsigh R., **The impact of Peyronie's disease on the patient: gaps in our current understanding.** J Sex Marital Ther 2016;42:178-190.
5. Levine L.A., **Seeking answers on the quest for effective nonsurgical treatment of Peyronie's disease.** Eur Urol 2007; 51:601-604.
6. Kendirci M., Hellstrom W.J., **Critical analysis of surgery for Peyronie's disease.** Curr Opin Urol 2004;14:381-388.
7. Abdel-Raheem A., Johnson M., Abdel-Raheem T., Capece M., Ralph D., **Sex Med Rev 2017**: 5:529-535.
8. Gelbard M.K.,Walsh R., Kaufman J.J., **Collagenase for Peyronie's disease experimental studies.** Urol Res 1982;10:135-140.
9. Gelbard M.K., Lindner A., Kaufman JJ. **The use of collagenase in the treatment of Peyronie's disease.** J Urol 1985; 134:280-283.
10. Gelbard M.K., Lindner A., Kaufman J.J., **The use of collagenase in the treatment of Peyronie's disease.** J Urol 1985; 134:280-283.
11. Gelbard M., Lipshultz L.I., Tursi J., et al., **Phase 2b study of the clinical efficacy and safety of collagenase clostridium histolyticum in patients with Peyronie's disease.** J Urol 2012; 187:2268-2274.
12. Gelbard M., Goldstein I., Hellstrom W.J., et al., **Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of Peyronie's disease in 2 large double-blind, randomized, placebo controlled phase 3 studies.** J Urol 2013; 190:199-207.
13. Levine L.A., Cuzin B., Mark S., et al., **Clinical safety and effectiveness of collagenase clostridium histolyticum injection in patients with Peyronie's disease: A phase 3 open-label study.** J Sex Med 2015;12:248-258.
14. Abdel Raheem A., Capece M., Kalejaiye O., Abdel-Raheem T., Falcone M., Johnson M., Ralph O.G., Garaffa G., Christopher A.N., Ralph D., **Safety and effectiveness of collagenase clostridium histolyticum in the treatment of Peyronie's disease using a new modified shortened protocol.** BJU Int. 2017; 120:717-723.
15. Ziegelmann M.J., Viers B.R., Montgomery B.D., Avant R.A., Savage J.B., Trost L.W., **Clinical experience with penile traction therapy among men undergoing collagenase clostridium histolyticum for Peyronie's disease.** Urology. 2017 Jun; 104:102-109.
16. Ralph D., Abdel Raheem A., Liu G., **Treatment of Peyronie's disease with collagenase clostridium histolyticum and vacuum therapy: a randomized, open-label pilot study.** J Sex Med 2017; 14:1430-1437.
17. Wymer K., Ziegelmann M., Trost L.,**Plaque calcification: an important predictor of collagenase clostridium histolyticum treatment success for men with Peyronie's desease.** J Urol 2018; 4S:e909.
18. Nguyen H.M.T., Anaissie J., DeLay K.J., Yafi F.A., Sikka S.C., Hellstrom W.J.G., **Safety and efficacy of collagenase clostridium histolyticum in the treatment of acute-phase Peyronie's disease.** J Sex Med. 2017 Oct; 14(10):1220-1225.

LI-ESWT in Andrology: A new intriguing opportunity to care for patients

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After the age of 40, a third of males has problems in achieving an erection. While psychological factors play a major role in erectile disorders in young people, in adulthood and old age organic problems have a greater responsibility in this disease (1). In healthy males, an erection is a complex event that causes changes in the muscles, nerves, and blood vessels of the penis. Instead, an erectile dysfunction (ED) occurs when the blood does not arrive or remain sufficiently in the penis thereby preventing to maintain a good erection (2).

The ED can be attributed to causes that can be largely distinghuised in psychological, neurogenic, endocrine, iatrogenic and vasculogenic. Research has documented several risk factors for ED, such as: age, cigarette smoking, alcohol and drug abuse, medications (antihypertensives, antidepressants, major tranquilizers, hormones, etc.), diabetes, obesity and dyslipidaemia, arterial hypertension, cardiovascular diseases, atherosclerosis, endocrinopathies, chronic systemic diseases (chronic renal failure, hepatopathies), central and peripheral neurological diseases, pelvic surgery (radical surgery for prostate, bladder, large intestine neoplasia) (3).

In particular, the vasculogenic ED is certainly the most frequent risk factor with a high prevalence (40%) in men with high cardiovascular risk as described in the Massachusetts Male Aging Study published in 1994 (4).

The first line of treatment for ED is the use of oral agents, such as 5 phosphodiesterase inhibitors to which, however, are linked some marked contraindications, such as the concomitant use of nitroderivatives. Although useful, the oral therapy is not able to act on the primus movens of the pathology but it has positive effects exclusively on the symptomatology (5).

The mechanism of function of low intensity shockwaves (Li-ESWT) has been able to act on the causal mechanism underlying ED. The mechanism by which they act is still not perfectly clear, but the most recent hypotheses state that LI-ESWT stimulate neoangiogenesis, recruit stem cells and help nerve regeneration by activating Schwann cells.

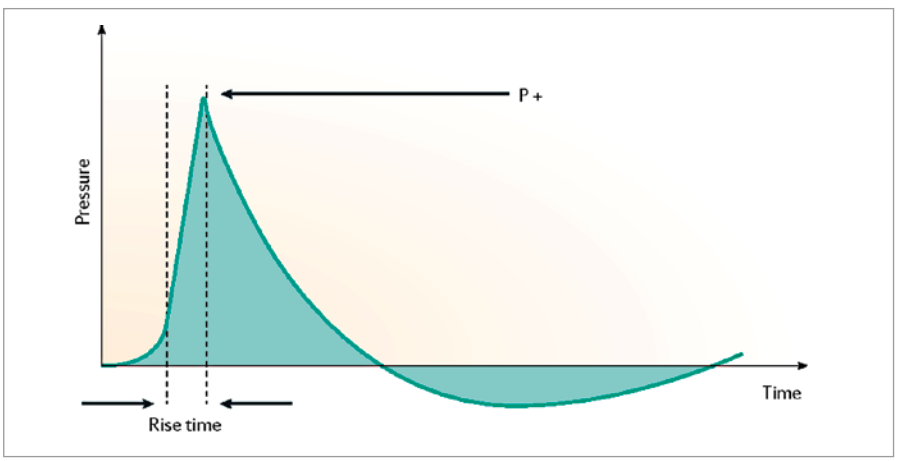

Figure1. Example of the schematic depiction of a shockwave as used in the treatment of ED. The figure illustrates a shockwave, i.e. a longitudinal acoustic wave made of a short pulse of about 5 µs duration, composed of an instantaneous jump to a positive acoustic peak pressure ('shock') followed by a longer-lasting period of negative pressure.

The shockwave is made of a longitudinal acoustic wave consisting of a short pulse of about 5 microseconds duration which has the characteristic of instantly reaching a positive pressure peak with a subsequent longer period of negative pressure (6) (Figure 1). This mechanism acts in two ways: it provokes a direct mechanical damage created by the wave itself and it creates a mechanism of swelling and subsequent collapse of bubbles inside blood vessels (7). The capillaries, i.e. smaller diameter vessels, are firstly involved, and then the larger vessels. Due to the formation and subsequent breakage of these micro-bubbles, a damage to the endothelium with associated vascular shear stress is provoked inside the capillaries. These "micro-traumas" trigger a recall of both progenitor cells and growth factors that elicit neo-angiogenesis (8) with the formation of new blood vessels formation (Figure 2).

It has been shown that in the rat hindlimb, shockwave provoked an upregulation of stromal cell-derived factor 1 (SDF-1) (9). SDF-1 is a ligand for CXCR-4, which is strongly expressed on endothelial progenitor cells (EPCs), and plays a crucial role in cell homing and function (10). In the rat ischaemic hindlimb model, combining shockwave therapy with perfusion of exogenous EPCs revealed additive effects in augmenting perfusion, showing that shockwaves increase neo-vascularization. Furthermore, shockwave therapy stimulate neuronal nitric oxide synthase (nNOS) enzymatic activity and NO production in neuronal cells in a dose-dependent fashion (11).

Several studies (Hausner et al. (12); Schuh et al. (13)) report positive effects of shockwave therapy on nerve regeneration, by supporting Schwann cell proliferation.

Different technological devices for treating the vasculogenic ED have been developed and classified, generally, into Focussed and Linear Li-ESWT. The Focussed Li-ESWT has the charac-

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teristic of generating and releasing the wave in a small area of the cavernous tissue. This creates the need for the operator to move along the penis (starting from the bottom) to treat the entire area including the crura penis.

According to different treatments adopted, several protocols have been developed (Table1)

Table 1:
Focused devices and treatment protocols

Omnispec ED1000, (medispec LTD.)	
DuolithSD1 Device (Storz Medical AG)	The study protocol included: 5 – 12 weekly session of 3.000 shocks each session
EFD: 0.15 – 0.25 mJ/mm2.	

Table 2:
Li-ESWT device and treatment protocol

linear Li-ESWT	Treatment protocols: four once-weekly sessions of 3.600 – 5000 shocks

The limit of focussed shockwaves is the need to treat different areas of the corpora cavernosa separately. For this reason, linear wave propagation devices have been developed and simultaneously cover a larger tissue surface. The latter treatment protocols need of a low amount of shockwaves for each therapeutic session (Table 2). Shockwave treatment was also used in subjects with radical prostatectomy. In fact, in these patients there is damage to the nerve fibres occurring close to the prostate. Studies have shown that in these patients there is a reduction of the erectile tissue due to the fibrosis following the lack of tissue oxygenation and for the inadequate organ perfusion (14,15). Two single-arm studies have explored low-intensity shockwave treatment in these patients: while a study does not provide adequate data to support the positive effect of shockwaves (16), another study shows that 7 of 16 patients increased their erectile function (17).

So far, no study has revealed adverse events (e.g., haematomas, haedemas, or abrasions) for shockwave treatment except for 1 patient who reported an allergic reaction to the gel used during treatment (18). Similarly, no follow-up data have been reported about the role of cavernous microtraumas predisposing putatively to fibrous plaque formation and the onset of IPP.

In conclusion, pharmacological therapies used for ED act on the symptomatology of the pathology by limiting, however, the complete autonomy of the patients to live their own natural sexual life. It was also observed that treating patients with Li-ESWT non-responders to PDE5i resulted in a partial response to subsequent pharmacological oral therapy with phosphodierasterase 5 inhibitors (PDE5i) (19). In addition, it has been suggested that the combination between physical shockwave treatment with PDE5i produce optimal therapeutic response (20). Few studies have been carried out on the various pathologies affecting patients undergoing shockwaves treatment and, in particular, on how these pathologies can influence the success of treatment. Another limitation of shockwaves treatment is the use of different devices (inducing wave generation procedures) and the diversity of protocols adopted. In the literature, there are no reliable data regarding the number of strokes to be used, the timing (weekly, monthly) and the intensity of the wave to be generated. Future, rigorous RCTs will better inform whether Li–ESWT is truly effective, and in what group of patients, lastly, low-intensity shockwaves also give us high hopes in the treatment of erectile dysfunction in diabetic patients. In fact, in these patients peripheral vascularization is impaired due to neuropathy. In these patients are formed due to hypoxia limb ulcers. In the literature there are few studies on the subject, but, a randomized and controlled study that evaluated shockwave therapy for diabetic ulcer, reports great benefits in healing of chronic ulcers by improving vascularization in the absence of side effects (21).

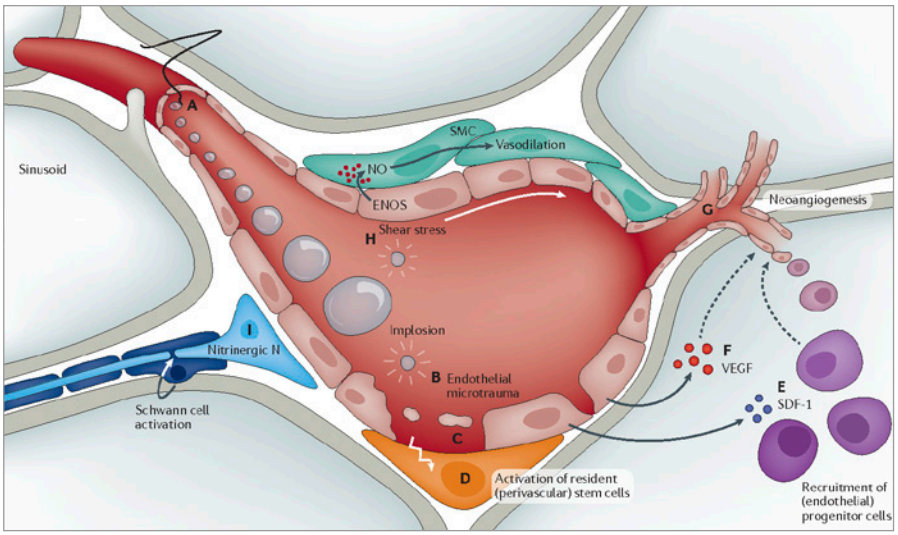

Figure 2. Example of shockwaves effects. The figure depicts an example of Shockwaves effects on microbubbles (A) in the vasculature and tissue that collapse (B) and cause disruption of the endothelium (C). Endothelial disruption might activate resident stem cells (D) and elicit chemokine production with attraction of (endothelial) progenitor cells (E) and release of VEGF (F); these factors combine to trigger neoangiogenesis (G). In addition, microbubble collapse induces shear stress and might stimulate endothelial NO production (H). Furthermore, shockwave therapy might also increase Schwann-cell-mediated nitrergic-nerve repair after injury (I) (drawn from Fade et al 2017, Nature Reviews).

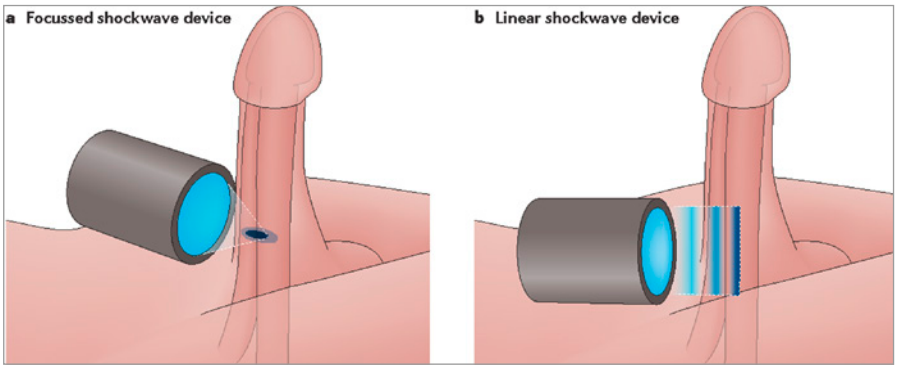

Figure 3: Figures depicting Focussed and Linear shockwave therapy. Focussed devices generated shockwaves to a focused area at a predetermined tissue depth. Linear shockwave devices generated shockwaves over a larger, linear shaped area at a predefined depth of penetration. Thus, a larger area of corporal

To sum up, the review of the literature showed that Li-ESWT is the first treatment option for ED that has the potential to improve pharmacologically unassisted erectile function. Furthermore, evidence has also suggested that the effects at molecular and tissue level are largely unknown, although neoangiogenesis might play a key role. Importantly, the UAE guidelines of 2018 (22) have indicated in their recommendations for ED treatment the use of Li-ESWT in patients with moderate ED, although with weak results. However, the literature is increasingly collecting encouraging results on the use of Li-ESWT with ED.

REFERENCES

1. Wessells H., Joyce G.F., Wise M., Wilt T.J., **Erectile dysfunction.** J Urol 2007; 177:1675-1681.
2. Shamloul R., Ghanem H., **Erectile dysfunction**. Lancet 2013; 381:153-165.
3. 4. Kubin M., Wagner G., Fugl-Meyer A.R., **Epidemiology of erectile dysfunction.** Int J Impot Res 2003;15:63-71.
4. Feldman H.A., Goldstein I., Hatzichristou D.G., Krane et al., **Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study**. J Urol 1994;151:54-61.
5. Bella A., Lee J., Carrier S., Benard F., 2015, **CUA guidelines for erectile dysfunction.** Can Urol Assoc J 2015;9(1-2):23-9.
6. Vardi Y., Appel B., Jacob G., Massarwi O., Gruenwald I., **Can low intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction.** Eur Urol 2010;58:243-248.
7. Bongrazio M. et al. **Shear Stress modulates expression of thrombospondin-1 and CD36 in endothelial cells in vitro and during shear stress-induced angiogenesis in vivo.** Int. J.immunopathol. Parmacol. 19, 35-48 (2006).
8. Belik D. et al., **Endothelium-derived microparticles from chronically thromboembolic pulmonary hypertensive patients facilitate endhotelial angiogenesis.** J. Biomed. Sci. 23, 462 (2016).
9. Aicher A. et al., **Low-energy shock wave for enhancingrecruitment of endothelial progenitor cells: a new modality to increase efficacy of cell therapy in chronic hind limb ischemia.** Circulation 114, 2823-2830 (2006).
10. Kucia M. et al., **CXCR4-SDF-1 signalling, locomotion, chemotaxis and adhesion.** J. Mol. Histol. 35, 233-245 (2004)
11. Ciampa A. R. et al., **Nitric oxide mediates anti-inflammatory action of extracorporeal shockwaves.** FEBS Lett. 579, 6839-6845 (2005).
12. Hausner T. et al., **Improved rate of peripheral nerveregeneration induced by extracorporeal shock wavetreatment in the rat.** Exp. Neurol. 236, 363-370 (2012)
13. Schuh C., Hausner T.,Redl H. R., **A therapeutic shockpropels Schwann cells to proliferate in peripheral nerve injury.** Brain Circul. 2, 138 (2016).
14. Weyne E., Castiglione F., Van der Aa F., Bivalacqua T. J., Albersen M., **Landmarks in erectile function recovery after radical prostatectomy.** Nat. Rev. Urol. 12, 289-297 (2015).
15. Iacono F. et al., **Histological alterations in cavernous tissue after radical prostatectomy.** J. Urol. 173,1673-1676 (2005).
16. Chung E., Cartmill R., **Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first openlabel single-arm prospective clinical trial.** BJU Int. 115 (Suppl. 5), 46-49 (2015)

LI-ESWT in Andrology: A new intriguing opportunity to care for patients

17. Frey A., Sønksen J., Fode M.,**Low-intensity extracorporeal shockwave therapy in the treatment of post prostatectomy erectile dysfunction: A pilot study.** Scand. J. Urol. 50, 123-127 (2015).
18. Gruenwald I., Appel B., Vardi Y., **Low-intensity extracorporeal shockwave therapy – a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy.** J Sex Med 2012; 9:259-264.Sex Med Rev 2018.
19. Kitrey N.D. et al., **Penile low intensity shock wavetreatment is able to shift PDE5i non responders to responders: A double-blind, sham controlled study.** J. Urol. 195, 1550-1555 (2016).
20. Palmieri A. et al., **Tadalafil once daily and extracorporeal shockwave therapy in the management of patients with Peyronie's disease and erectile dysfunction: Results from a prospective randomized trial.** Int. J. Androl. 35, 190-195 (2011).
21. Omar M.T., Alghadir A., Al-Wahhabi K.K., Al-Askar A.B., **Efficacy of shockwave therapy on chronic diabetic foot ulcer: a single-blinded randomized controlled clinical trial.** Diabetes Res Clin Pract. 2014 Dec;106(3): 548-54. Oct 5.
22. Hatzimouratidis K. (Chair), Giuliano F., Moncada I., Muneer A.,Salonia A. (Vice-chair), Verze P., *Guideline Associates: Parnham, A., Serefoglu E.C.,* **EAU Guidelines 2018: Male sexual dysfunction**.

Have You Read? Best of the Best: Clinical Research

by Bruno Jorge Pereira and Nuno Louro

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Men's Health

Rochira V., Antonio L., Vanderschueren D. **EAA Clinical Guideline on Management of Bone Health in the Andrological Outpatient Clinic.** Andrology 2018 Mar;6(2):272-285.

Male osteoporosis is now a well-recognized medical disorder with established clinical guidelines for both diagnosis and management. Andrologists should therefore be aware of the potential silent presence of osteoporosis in men with confirmed hypogonadism. Such bone health assessment should include medical history and physical examination related to fracture risk. Furthermore, dual-energy absorptiometry is indicated to evaluate fracture risk in men with hypogonadism. Regarding treatment, besides general measures to prevent or manage male osteoporosis testosterone replacement can be initiated but data on its efficacy in preventing fractures is lacking. Thus, additional anti-osteoporotic may be needed, especially in men with very low testosterone who are at high risk of bone loss or in men not able to receive testosterone replacement.

Sexual Function

Awad M.A., Gaither T.W., Murphy G.P., et al. **Cycling, and Male Sexual and Urinary Function: Results from a Large, Multinational, Cross-Sectional Study.** J Urol. 2017 Oct 13 [Epub ahead of print].

Cyclists were recruited to complete a survey through Facebook advertisements and outreach to sporting clubs. Swimmers and runners were recruited as a comparison group. Cyclists were categorized into low and high intensity cyclists. Participants were queried using SHIM, IPSS and NIH-CPSI. Complete survey responses 3.932 were included. Cyclists had no worse sexual or urinary functions than swimmers or runners but cyclists were more prone to urethral stricture. Increased time standing while cycling and a higher handlebar height were associated with lower odds of genital sores and numbness.

Erectile Dysfunction

Corona G., Maggi M., Jannini E.A. **EDEUS, a Real-Life Study on the Users of Phosphodiesterase Type 5 Inhibitors: Prevalence, Perceptions, and Health Care-Seeking Behavior among European Men with a Focus on 2nd Generation Avanafil.** Sex Med 2018; 6:15-23.

This study evaluated the real-life characteristics and unmet needs of men with ED, its impact on well-being, and treatment rates across Europe. IIEF-15 with study-specific, self-constructed questions was used. 940 subjects were considered. Subjects using on-demand PDE5is were designated "performers" (60%) without a formal ED diagnosis or "patients" with a medical diagnosis. Patients were older than performers, with more self-reported comorbidities; patients used a higher PDE5i dosage and purchased it from official pharmacies more often than performers did. The survey shows two different attitudes toward ED and PDE5i use: for recreational use and without a medical prescription or with a formal diagnosis and medical prescription. Avanafil, a 2nd-generation PDE5i with a good balance between efficacy and tolerability profile, is more frequently prescribed by doctors than self-prescribed compared with other PDE5is.

Ralph D.J., Eardley I., Taubel J., et al. **Efficacy and Safety of MED2005, a Topical Glyceryl Trinitrate Formulation, in the Treatment of Erectile Dysfunction: A Randomized Crossover Study.** J Sex Med 2018; 15:167-175.

Current treatments for erectile dysfunction (ED) have some limitations. This study evaluated the efficacy and tolerability of MED2005, a 0.2% glyceryl trinitrate topical gel, administered on demand, in the treatment of ED. This randomized, double-blinded, placebo-controlled, phase II crossover trial involved 232 men with ED and their partners. Efficacy was assessed by the IIEF, SEP and GAQ. Overall, 23.1% of patients showed a clinically relevant (>4-point) increase in IIEF-EF scores after treatment with MED2005. Significant effects of MED2005 were seen primarily in patients with mild ED. The start of erection was noticed within 5 and 10 minutes in 44.2% and 69.5%, respectively. The most commonly reported adverse events during MED2005 were headache (7.9%) and nasopharyngitis (5.7%). These findings suggest that topical glyceryl trinitrate could be a useful treatment option in ED but further studies are warranted to investigate the efficacy of higher doses, thereby improving clinical significance, especially in cases of moderate and severe ED.

Sexual Rehabilitation

Siena G., Mari A., Canale A., et al. **Sexual Rehabilitation After Nerve-Sparing Radical Prostatectomy: Free-of-Charge Phosphodiesterase Type 5 Inhibitor Administration Improves Compliance to Treatment.** J Sex Med 2018; 15:120-123.

This prospective study intended to compare sexual rehabilitation outcomes in patients with low risk of erectile dysfunction and minimal comorbidities who received PDE5Is

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free of charge (PDE5I-F) with those who paid for PDE5Is (PDE5I-P) after bilateral NSRP in Tuscany from 2008 to 2013, based on EDITS and UCLA-PCI-s questionnaires. The PDE5I-F group had a significantly higher early rehabilitation onset, lower treatment dropout at 12, 24, and 36 months and higher compliance to the treatment protocol at 6 and 12 months. The free-of-charge protocol was significantly associated with higher early rehabilitation onset, major compliance to the protocol, minor treatment dropout, and higher satisfaction rate of patients.

Testosterone and Sexual Endocrinology

Corona G., Rastrelli G., Di Pasquale G., et al. **Testosterone and Cardiovascular Risk: Meta-Analysis of Interventional Studies.** J Sex Med 2018; 15:820-838.

The relationship between testosterone (T) and cardiovascular (CV) risk in men is conflicting. The authors conducted a random effect meta-analysis considering all available data from pharmaco-epidemiological studies as well as randomized placebo-controlled trials to investigate CV mortality and morbidity. 15 pharmaco-epidemiological and 93 RCT studies were considered. The analysis of pharmaco-epidemiological studies documented that TTh reduces overall mortality and CV morbidity. Conversely, in RCTs, TTh had no clear effect, either beneficial or detrimental, on the incidence of CV events. However, a protective role of TTh on CV morbidity was observed when studies enrolled obese (BMI >30 kg/m^2) patients. An increased risk of CV diseases was observed in RCTs when T preparations were prescribed at dosages above those normally recommended, or when frail men were considered. Data from RCTs suggest that treatment with T is not effective in reducing CV risk, however, when TTh is correctly applied, it is not associated with an increase in CV risk and it may have a beneficial effect in some sub-populations.

Ruiz-Olvera S.F., Rajmil O., Sanchez-Curbelo J.R., et al. **Association of Serum Testosterone Levels and Testicular Volume in Adult Patients.** Andrologia. 2018 Apr; 50(3).

A retrospective observational study was undertaken to gain new insight into the relationship between total testicular volume (TTV) and levels of serum T, LH, FSH, prolactin and clinical variables. A total of 312 men with sexual dysfunction or infertility were divided into groups A and B based on basal plasma T ≤5 nmol/L of ≥12 nmol/L respectively. Group A was subclassified in A1 (primary hypogonadism) and A2 (secondary hypogonadism). There were significant differences in TTV between group A (15.33 ± 11.94 ml) and B (36.74 ± 6.9; $p < .001$) and also between A1 (11.07 ± 8.49 ml) and A2 (23.62 ± 13.04 ml; $p < .001$). Only 13.5% of patients in group B had a TTV < 30 ml. Differences in all studied parameters were found between group A and group B. There were no variations when comparing age, BMI and T in groups A1 and A2. The use of TTV and BMI together for predicting T levels yields a sensitivity and specificity of 85.3% and 86.5% respectively.

Zitzmann M. **Would Male Hormonal Contraceptives Affect Cardiovascular Risk.** Asian Journal of Andrology (2018) 20, 145-148.

Hormonal male contraception (HMC) is based on the principle that exogenous administration of androgens and other hormones such as progestins suppress circulating gonadotropin concentrations, decreasing testicular Leydig cell and Sertoli cell activity and spermatogenesis. In order to achieve more complete suppression of circulating gonadotropins and spermatogenesis, a progestin has been added testosterone to the most recent efficacy trials of HMC. This review focusses on the potential effects of HMC on cardiovascular (CV) risk factors, lipids and body composition, mainly in the target group of younger to middle-aged men. Present data suggest that HMC can be reasonably regarded as safe in terms of CV risk. However, as all trials have been relatively short (< 3 years), a final statement regarding the CV safety of HMC, especially in long-term use, cannot be made.

Ejaculatory Disorders

Cho M.C., Kim J.K., Song S.H., et al. **Patient-Reported Ejaculatory Function and Satisfaction in Men with Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia.** Asian Journal of Andrology (2018) 20, 69-74.

A total of 1574 treatment-naïve men with LUTS/BPH were included in this study to investigate perceived ejaculatory function/satisfaction before treatment. Decreased ejaculatory volume and force were reported by 53.4% and 55.7% of 783 sexually active men, respectively. There was a strong correlation between ejaculatory volume and force. Ejaculatory pain/discomfort, premature ejaculation (PE), and delayed ejaculation (DE) were reported in 41.0%, 16.3%, and 41.4% of the patients, respectively. Over 40.0% of men without decreased ejaculation volume/force were satisfied with ejaculatory function, whereas approximately 6.0% of men with decreased volume/force were satisfied with ejaculatory function. About 30.0% of men with decreased volume/force had orgasmic dysfunction, while approximately 10.0% of men without decreased volume/force did. Decreased ejaculatory volume or force was associated with LUTS severity.

ACUTE SCROTUM

Bitkin A., Aydın M., Özgür B.C, et al. **Can Haematologic Parameters be Used for Differential Diagnosis of Testicular Torsion and Epididymitis?** Andrologia. 2018 Feb; 50(1).

In emergency conditions, if testicular torsion goes unnoticed and epididymo-orchitis is diagnosed, organ loss may occur. Patients (n=153) were divided into three groups as those undergoing surgery for testicular torsion, those receiving medical treatment for epididymitis

and a healthy control group. All patients had complete blood counts taken with determinations of mean platelet volume (MPV), platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR) and leucocyte counts. Leucocyte, MPV and NLR values were higher in both the epididymitis and torsion groups compared to controls. Platelet counts and PLR were significantly higher in the epididymitis group compared to the other two groups. Leucocyte, MPV and NLR values may be used in the diagnosis of epididymitis and testicular torsion.

Surgery

Wilson S. **The Top 5 Surgical Things that I Wish I had Known Earlier in my Career: Lessons Learned from a Career of Prosthetic Urology.** J Sex Med. 2018 Jun;15(6): 809-812.

In this invited commentary the internationally recognized urologist in prosthetic surgery, Steve Wilson, shares his top 5 surgical lessons learned from a 45-year practice in the field: never implant a stranger, treat erectile dysfunction and Peyronie's disease with IPP, ectopic reservoir placement is safer, never rush to revise an IPP and his journey to the AMS "1500" and back where even though he invented the dual implant via single-incision, he now discourage it.

Ziegelmann M.J., Alom M., Bole R., et al. **Modified Glanulopexy Technique for Supersonic Transporter Deformity and Glanular Hypermobility in Men with Penile Prostheses.** J Sex Med 2018;15:914-919.

Glanular hypermobility (GH) or supersonic transporter (SST) deformity are occasionally encountered during penile prosthesis (PP) implantation. This article describes a simple modified technique for glanulopexy to correct GH/SST during PP placement without reduced penile sensation, whereby a suture is passed into the glans and anchored to the tissue overlying the corpora through small incisions on the lateral aspects of the distal penile shaft.

Habous M, Tal R, Tealab A, et al. **Defining a Glycated Haemoglobin (HbA1c) Level that Predicts Increased Risk of Penile Implant Infection.** BJU Int. 2018 Feb;121(2):293-300.

A multicentre prospective study including 902 penile implant procedures (76% malleable and 24% inflatable) in patients with a mean age of 56,6 years (2009 to 2015). The HbA1c levels were analyzed as continuous variables and sequential analysis was conducted using 0.5% increments to define a threshold level predicting implant infection. The overall infection rate was 8.9% (80/902). Patients who had implant infection had significantly higher mean HbA1c levels, 9.5% vs 7.8%. Grouping the cases by HbA1c level, we found infection rates were: 1.3% with HbA1c level of <6.5%, 1.5% for 6.5–7.5%, 6.5% for 7.6–8.5%, 14.7% for 8.6–9.5%, 22.4% for >9.5% ($P < 0.001$). Predictors defined on multivariable analysis were: PD, high BMI, and high HbA1c level, whilst a high-volume surgeon had a protective effect and was associated with a reduced infection risk. Using ROC analysis, a HbA1c threshold level of 8.5% predicted increased infection risk with a sensitivity of 80% and a specificity of 65%.

Falcone M., Preto M., Ceruti C., et al. **A Comparative Study Between 2 Different Grafts Used as Patches after Plaque Incision and Inflatable Penile Prosthesis Implantation for End-Stage Peyronie's Disease.** J Sex Med 2018 Jun;15(6):848-852

Many grafts have been used for plaque incision with grafting (PIG) and penile prosthesis (PP) implantation but there is no evidence that favors one specific graft over another. In this non-randomized study fibrin-coated collagen fleece (TachoSil) (group B, 26 patients) was compared with porcine small intestinal submucosa (SIS) (group A, 34 patients) as grafts. No major intraoperative complications were reported. The average operative time was 145 minutes for group A and 120 minutes for group B. No statistically differences were detected for postoperative complications and TachoSil seems to represent an effective solution for grafting after PIG and PP implantation.

Andrology on the Internet

Baunacke M, Groeben C, Borgmann H. Andrology on the Internet: **Most Wanted, Controversial and Often Primary Source of Information for Patients.** Andrologia. 2018 Mar; 50(2).

The Internet is an important source of health information with relevant impact on the physician–patient relationship. The German urological associations invited users of the website www.urologenportal.de to complete a 26-item online survey to evaluate health-related behaviour, distress and decision-making preferences. 551 completed responses. The most frequently requested topics were from the field of andrology (45.4%, n = 250). Of these, the most popular topics were circumcision (28.9%, n = 159) and erectile dysfunction (18.1%; n = 100). Overall, 216 users (39.2%) searched for information prior to their first doctor's appointment, and 89.3% (n = 492) preferred autonomous or shared decision-making. Andrology was the most frequently requested urological topic. This might have an impact on the physician-patient relationship and causes a high demand for good-quality health information websites.

MEETINGS AND EVENTS CALENDAR 2018/2019

Dr. Roberto Larocca
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September

4th Biennial Meeting of the South Asian Society for Sexual Medicine
13 – 15 September 2018
Bangalore, India
www.sassm.in

November

2018 SMSNA
Annual Fall Scientific Meeting
8 – 11 November 2018
Miami, FL, USA
www.smsna.org

ISSWSH Fall Course 2018
15 – 17 November 2018
Scottsdale, AZ, USA
www.isswshcourse.org

January 2019

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

March 2019

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

EAU Annual Meeting 2019
15 – 19 March 2019
Barcelona, Spain
www.uroweb.org

May 2019

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

October 2019

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

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

November 2019

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

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