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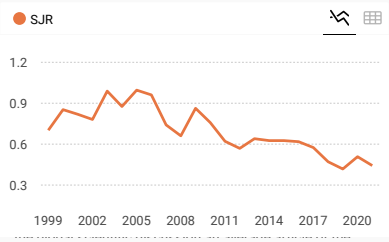

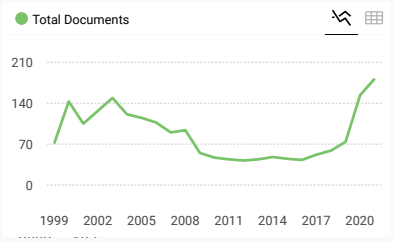

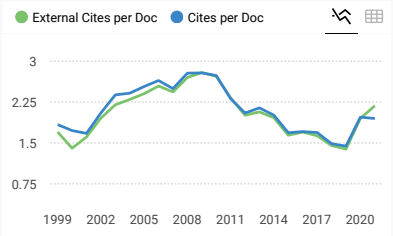

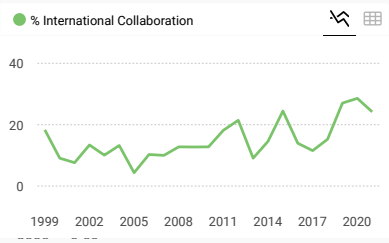

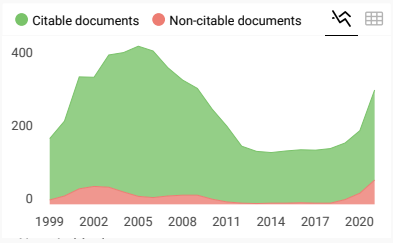

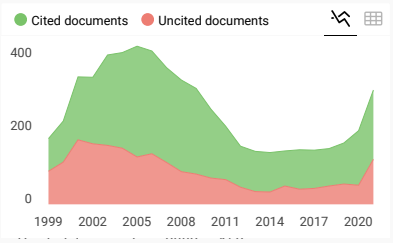

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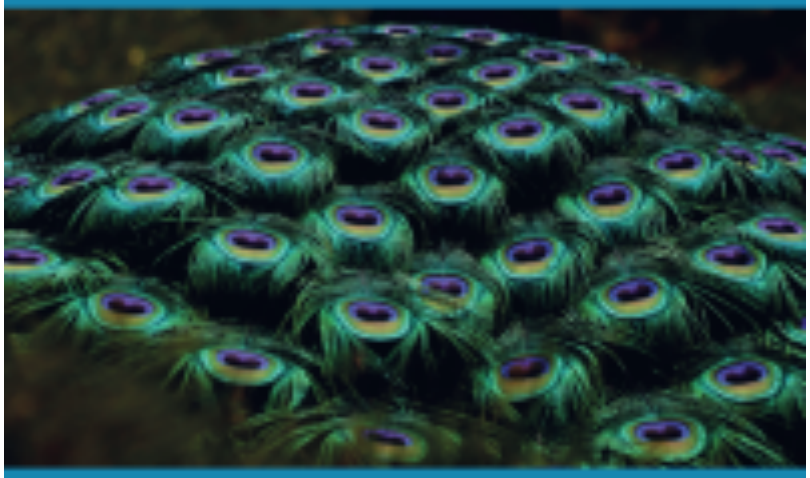

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About the Editors

Editor-in-Chief

Ege Can Serefoglu, MD, Biruni University School of Medicine, Turkey

Ege Can Serefoglu received his Medical Doctor degree from Turkey and followed this with a residency in urology. After practicing as a urologist for 2 years, he has then worked as a post-doctorate research fellow at Tulane University Department of Urology, Division of Andrology, USA. He received the "Amsterdam Young Scientist Award" in 2012 and he is actively working in professional organizations such as Turkish Association of Urology, European Association of Urology (EAU), European Society for Sexual Medicine (ESSM) and International Society of Sexual Medicine (ISSM), as well as working as a private urologist in Turkey.

Watch a video from Ege about *IJIR: Your Sexual Medicine*

Devi Ahilya University, Indore, India. He was awarded the Korean Government Scholarship for PhD degree in molecular Biology from National Institute of International Education [NIIED]. He was the recipient of Brain Korea 21 [BK21] scholarship in 2009-2010 for a period of six months from Seoul National University for the superior performance in research and development. Then he was awarded Young Investigator award from Regional center for Biotechnology, DBT, India where he worked on the mechanisms of resistance development in colorectal cancer before moving to CNRS, France, where he spent two years as a Postdoc and explored regenerative mechanisms in cardiovascular biology. He joined the University of Miami in 2016 as a Postdoc fellow where he explored the role of nitric oxide donors and their anti-inflammatory and anti-proliferative effects on tumor microenvironment of castration resistant prostate cancer. He received the American Urological Research Scholar Award (2020). Dr Arora joined University of Miami faculty in 2019 and his current focus is on 1) Exploring therapeutic efficacy of Nitric oxide donors (Immunotherapy) against different stages of Prostate cancer progression, 2) Using Nitric oxide donors in combination with currently available immune checkpoint inhibitors like PD-L1 inhibitors, MIA series compounds, CSF1R inhibitors, 3) using machine learning tools to study the progression of prostate cancer and applying this knowledge in building up translational tools that could be used by researchers, clinicians and patients. Dr Arora has been a speaker at many international (ASRM, AUA, SMSNA) and National congresses in the field of andrology, sexual medicine and uro-oncology

Luca Boeri, MD, Foundation IRCCS Ca' Granda Policlinico Hospital, Milan, Italy

Luca Boeri is a Urologist and Andrology at

Foundation IRCCS Ca' Granda, Policlinico Hospital of Milan, Italy. In November 2019 he started his PhD program in Clinical Research at University of Milan focusing on couple's infertility, genetics and immunology. He received his medical degree at Vita-Salute San Raffaele University in Milan, Italy, in 2014. During his residency program he attended a visiting fellowship at University College London Hospital (Prof. David Ralph), UK, and he also completed a research fellowship at Mayo Clinic (Mentor Dr. R. Jeffrey Karnes), Rochester, USA, where he attended a one-year advanced statistics course.

Since 2014 he continued a successful collaboration with the Urological Research Institute-URI of Milan under the guide of Prof. Montorsi and Prof. Salonia. His specialty areas include sexual medicine, infertility, uro-oncology and minimally invasive surgical techniques. He is an active member of the Italian Society of Andrology where he is part of the WEB group. He is now member of the EAU Guideline Panel on Sexual and Reproductive Health.

Brian D. Earp, PhD, University of Oxford, Oxford, UK

Dr. Earp received his PhD from Yale University jointly in experimental psychology and philosophy, focusing on relationship norms, gender, sexuality, and bioethics. He is co-editor of *The Routledge Handbook of Philosophy of Sex and Sexuality* (Routledge, 2022), and co-author of *Love Drugs: The Chemical Future of Relationships* (Stanford University Press, 2020), the latter of which investigates the science and ethics of drug-assisted couples therapy. A recipient of the 2018 Daniel M. Wegner Theoretical Innovation Prize from the Society for Personality and Social Psychology, Brian was also one of four named finalists for the 2020 John Maddox Prize for "standing

up for science" (awarded by Sense about Science and *Nature*). Prior to commencing his doctoral studies, Brian completed a master's degree in the history, philosophy, and sociology of science, technology, and medicine at the University of Cambridge, and a master's degree in psychological research methods at the University of Oxford. His first degree was in cognitive science from Yale. Having served as the inaugural Presidential Scholar in Bioethics at The Hastings Center in New York, Brian is now Associate Director of the Yale-Hastings Program in Ethics and Health Policy at Yale University and The Hastings Center, and a Senior Research Fellow in Moral Psychology at the Uehiro Centre for Practical Ethics at the University of Oxford.

J Scott Gabrielsen, PhD, University of Rochester School of Medicine and Dentistry, United States

Scott Gabrielsen is an Assistant Professor at the University of Rochester School of Medicine and Dentistry, where he splits his time between clinical practice and basic science/translational research. He completed medical school at the University of Utah. While there, he also earned a PhD in Biochemistry. His dissertation work investigated the effects of dietary iron on insulin sensitivity in humans and mice. He completed his Urology residency training in the Harvard Urologic Surgery Residency Program at the Massachusetts General Hospital in Boston, MA, and subsequently completed a 2-year Fellowship in Male Reproductive Medicine and Surgery at Baylor College of Medicine in Houston, TX. His current research focuses on how diet and lifestyle affect male reproductive health.

Murat Gul, MD, Selcuk University School of Medicine, Turkey

Murat Gul received his Medical Doctor degree from Turkey and finished his urology residency at the same university. After working as a urologist for 3 years, he started his post-doctorate andrology fellowship program at Copenhagen University, Juliane Marie Centre for Women, Children and Reproduction, Laboratory of Reproductive Biology. Then he started his new position as an Assistant Professor at Selcuk University, Department of Urology. Alongside his position at university, he has been an associate member of the EAU Guidelines Panel on Sexual and Reproductive Health since 2019. He also serves as a member of EAU-YAU Men's Health Working Group and ESSM New Technologies and Sexual Function Committee. His scientific and clinical areas of interest are male infertility and male sexual dysfunctions.

James Hotaling, The University of Utah, USA

Dr. Hotaling is a fellowship trained andrologist. He is currently an Associate Professor of Surgery (Urology) at The University of Utah and serves as the co-director of the Surgical Analysis Population Research Core (SPARC), director of men's health and urologic research programs and fellowship director. He completed his undergraduate at Dartmouth College with a double major in biophysical chemistry and history, medical school at Duke University and residency at The University of Washington in 2012 where he also completed an MS in clinical epidemiology with a focus on statistical genetics. He has a clinical practice consisting of male infertility, sexual medicine and transgender surgery. He has over 190 publications, multiple book chapters, has given invited lectures all over the world and holds multiple societal leadership

positions. He also has multiple NIH grants with a focus on the genetics of ED, home uroflowimetry, germline de novo mutation rate in infertile men, single cell RNA sequencing of human testicular tissue and the heritability of male infertility as it relates to somatic health. He has also founded multiple startup companies.

Odunayo Kalejaiye, MBBS BSc MRCS FRCS (Ed), Heartlands, Good Hope & Solihull Hospitals (part of University Hospitals Birmingham NHS Foundation Trust), UK

Odunayo Kalejaiye is a Consultant Urological Surgeon, specialising in benign and malignant conditions of the penis and scrotum. Odunayo currently works at University hospitals Birmingham where she has been a Consultant since 2017. She is currently the clinical lead for penile cancer cases and benign andrology for the West Midlands, England. She is also one of only two surgeons in the West Midlands providing penile implant surgery. Odunayo has played a key role in modernising the andrological services in Birmingham.

Odunayo graduated from University College London in 2003 with a medical degree and a bachelor's degree with Honours in molecular medicine. After completing her specialist registrar training in South West England, she undertook a 2 year fellowship in one of the largest dedicated andrology centres in Europe (University College London). During her fellowship, she gained a wide exposure and training in a variety of andrological conditions in both emergency and non-emergency settings.

Miss Kalejaiye has been involved in patient engagement projects, presentations locally and internationally and publications for medical journals. She is regularly involved in training colleagues locally as well as on formal courses organised by the national urology body. Lastly, she is currently the secretary for BAUS

Andrology

Mujde Ozer, PhD, Amsterdam University Medical Center, Netherlands

Müjde Özer is both a Plastic Surgeon and Sexologist at the Amsterdam University Medical Center, location Vumc in the Netherlands. She has been associated with the department of Plastic, Reconstructive and Hand surgery since 2012. Müjde studied medicine at the Radboud university in Nijmegen after which she specialized as a plastic, reconstructive and hand surgeon at the AMC in Amsterdam. During the first 2 years of her training as a Plastic surgeon she also specialized in Sexology, got her post-master degree in 2008 and also became a Fellow of the European Committee of Sexual Medicine (FECSM) in 2012.
Both her scientific and clinical fields of interest are genital alteration, transgender surgery, reconstructive genital surgery, all approached with a sexologist background.
Although gender surgery and in genital reconstructions are in her main tasks, she is also skilled in general reconstructive surgery, oncodermatology and hand surgery.

Premal Patel, MD, University of Manitoba, Canada

Dr. Premal Patel joined the Section of Urology at the University of Manitoba in July 2019 as an Assistant Professor. He completed his Fellowship training in Male Infertility, Microsurgery & Sexual Medicine at the University of Miami. He has published numerous peer-reviewed manuscripts in the field of Male

Reproductive Urology. Prior to completing his Fellowship, Dr. Patel completed his Urology Residency at the University of Manitoba and obtained his Medical Degree from the University of Calgary.

Javier Romero-Otero, Phd, 12th October University Hospital, Spain

Javier Romero-Otero MD PhD FEBU FECSM, graduated in Urology in Madrid in 2006. Later he was fellow Memorial Sloan Kettering Cancer Center (NYC) 2006-2007. He subsequently returned to Spain where he developed his PhD. He has developed his care activity at the 12th October University Hospital (Madrid), where he is currently in charge of the Andrology and Reconstructive Surgery Unit of the male genital area (reference center in Spain). He is also the head of Urology at HM Hospitales in Madrid. In the teaching field, he is a professor of Urology at the Complutense University and at the San Pablo CEU University in Madrid. He is also director of the University Master of Andrology and Reconstructive Surgery of the male genital area at the University of Salamanca. Professor in the Academic Master "Human Infertility" in Complutense University. Professor in the Academic Master "Urethral Surgery" International University of Andalucia. In the field of research, he is the director of the Instituto de Salud Integral del Hombre of the Community of Madrid I + D + i. He has also been coordinator of the Andrology group of the Spanish Association of Urology, he is a member of the Board of Reconstructive Surgery of the European Urological Association, and member of the executive committee of the ESSM.

Giorgio Russo, Phd, University of Catania, Italy

Giorgio Russo is a PhD Urologist at the

University of Catania and has been a Research and Clinical fellow in the Department of Urology at the University of Tübingen with Prof. A. Stenzl since July 2017. He graduated as a Urologist with 70/70 and honors in July 2017 at the University of Catania with the Chairman Prof. Giuseppe Morgia. Since November 2016, he has been undertaking a Phd in translational biomedicine at the University of Catania and from March 2018 he became a teaching assistant in Urology at the University of Catania. alongside this Dr Russo has been a member of the EAU Young Academic Urologists – Men's Health working group and Referent of the Scientific Working Group of the Communication Office of the Società Italiana d'Urologia (SIU) since October 2017. Dr Russo is also a statistical analyst at the Urological clinic of the University of Catania with many publications to his name (https://www.ncbi.nlm.nih.gov/pubmed/?term=russo+gi), as well as being a speaker at many international (EAU, AUA, SIU) and National congresses in the field of andrology, sexual medicine and uro-oncology.

Ioannis Sokolakis, MD, Medical School of Aristotle University of Thessaloniki, Greece

Dr. Ioannis Sokolakis is an Assistant Professor of Urology in the Medical School of Aristotle University of Thessaloniki, Greece (2022). He graduated from the Medical School of Aristotle University of Thessaloniki in 2007. He has a Master of Science (M.Sc.) in medical research methodology (2012), and Ph.D. in Medicine (Urology/Sexual Medicine) (2018). He is a Fellow of the European Board of Urology (FEBU) since 2015 and a Fellow of the European Committee of Sexual Medicine (FECSM)

since 2020. He has been specialized in sexual medicine and reconstructive urology at the Aristotle University of Thessaloniki, Greece as well as the University of Wuerzburg, Germany. Besides sexual medicine and reconstructive urology, his current clinical interest involves robotic surgery and surgical urologic oncology. His main research interests are sexual medicine (erectile dysfunction and Peyronie's disease) as well as urological malignancies including bladder and prostate cancer. He is a member of the Young Researchers Committee of the International Society of Sexual Medicine (ISSM), a member of the European Society of Sexual Medicine (ESSM) Scientific Committee, and a member of EAU's Young Academic Urologists (YAU) Sexual and Reproductive Health Group.

Paolo Verze, MD, University of Naples Federico II School of Medicine and Surgery, Italy

Dr. Paolo Verze was born in Napoli on 25th June 1977. He is an Assistant Professor in the Department of Urology at the University of Naples Federico II School of Medicine and Surgery based in Naples, Italy where he received his medical degree and completed his residency training in Urology. He subsequently completed his doctorate degree (PhD) in urological sciences at the University of Palermo. His specialty areas include sexual medicine, uro-oncology and minimally invasive surgical techniques (robotic and laparoscopic). Dr. Verze is Chairman of the Men's Health group of the EAU's Young Academic Urologist (YAU) working party, Member of the EAU Guideline panel on Male sexual dysfunctions, Member of the ESSM Executive Committee and Associate Editor of the International Journal for Impotence Research (IJIR). He is author of about 90 original articles and a number of books, chapters, monographs and international abstracts.

Emmanuel Weyne, MD, KU Leuven University, Belgium

Dr Emmanuel Weyne received his Medical Doctor degree at the KU Leuven University in Leuven, Belgium and is currently finishing a residency in Urology at the same institution. He obtained the degree of doctor in the biomedical sciences by investigating the role of neurotrophic factors in nerve regeneration after cavernous nerve injury in a preclinical model mimicking erectile dysfunction after radical prostatectomy. His research he has been awarded multiple times at national and international conferences, among which is the prestigious Zorgniotti-Newman prize awarded by the International Society for Sexual Medicine (ISSM). He serves as a member of the Basic Science Sub-Committee for the European Society for Sexual Medicine (ESSM).

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ARTICLE

Intratunical injection of autologous adipose stromal vascular fraction reduces collagen III expression in a rat model of chronic penile fibrosis

Lukman Hakim[1,2] · Salvatore Fiorenzo[3] · Petter Hedlund[4,5] · Francesco Montorsi[6] · Trinity J. Bivalacqua[7] · Dirk De Ridder[1] · Emmanuel Weyne[1] · David Ralph[8] · Giulio Garaffa[8] · Asif Muneer[8,9] · Steven Joniau[1] · Maarten Albersen[1] · Fabio Castiglione[1,6,8] · On behalf of the Trauma and Reconstructive Urology Working Party of the European Association of Urology (EAU) Young Academic Urologists (YAU)

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Abstract

Previous studies have shown that the injection of adipose stem cells and stromal vascular fraction(SVF) into the tunica albuginea (TA) during the inflammatory phase in a rat model of Peyronie's disease(PD) prevented the development of TA fibrosis. Our aim was to investigate whether local injection of SVF can reduce established fibrosis in a rat model of chronic phase of PD. Eighteen-male 12-wk-old Sprague-Dawley rats were divided in three equal groups: sham, PD without treatment (PD) and PD treated with SVF(PD-SVF). Sham rats underwent 2 injections of vehicle into the TA one month apart. PD rats underwent TGF-β1 injection and injection of vehicle one month later. PD-SVF rats underwent TGF-β1 injection followed by SVF (1-million cells) one month later. One month after the last treatment, the animals, $n = 6$ rats per group, underwent measurement of intracorporal and mean arterial pressure during electrostimulation of the cavernous nerve. Following euthanasia, penises were harvested for in-vitro study. Erectile function was not statistically significantly different between groups. PD animals developed subtunical areas of fibrosis and elastosis with upregulation of collagen III protein. These fibrotic changes were reversed after injection of SVF. We provide evidence that local injection of SVF reverses TA fibrosis in a rat model of chronic phase of PD.

Introduction

Fibrosis is defined by an excessive accumulation of extracellular connective tissue proteins (extracellular matrix (ECM)) such as collagen, elastin and fibronectin [1]. Typically, ECM aggregation is an indispensable and reversible phase of the wound healing process [2]. It can, however, progress into long-lasting fibrotic response if the wound-healing process itself becomes deregulated [3]. Fibrosis represents the final, usual pathological result of many chronic inflammatory conditions [1, 4]. Peyronie's Disease (PD) is an acquired fibrotic disorder involving the tunica albuginea (TA)

✉ Maarten Albersen
maartenalbersen@hotmail.com

[1] Laboratory for Experimental Urology, Organ systems, Department of Development and Regeneration, University of Leuven, Leuven, Belgium

[2] Department of Urology, Airlangga University / Dr Soetomo General Hospital, Surabaya, Indonesia

[3] Facoltà di Medicina e Chirurgia, Unversitá Degli Studi di Palermo, Palermo, Italy

[4] Department of Clinical and Experimental Pharmacology, Lund University, Lund, Sweden

[5] Division of Drug Research, Department of Medical and Health Sciences, Linköping University, Linköping, Sweden

[6] Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy

[7] The James Buchanan Brady Urological Institute, Department of Urology, Johns Hopkins Medical Institutions, Baltimore, MD, USA

[8] The Institute of Urology, University College of London Hospital (UCLH), London, UK

[9] Division of Surgery and Interventional Science and NIHR Biomedical Research Centre University College London Hospital, London, UK

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of the penis and leading to the formation of fibrous plaques, penile curvature, pain and rarely erectile dysfunction [5].

Commonly, PD is classified into an acute (or inflammatory) phase and a chronic (or stable) phase. During the former, there may be penile pain and a penile deformity may become visible during erection. Penile pain resolves spontaneously within 12–18 months of PD onset in most patients [5]. During the chronic phase pain is absent and the curvature is stabilized [6].

In the last decade, several preclinical studies have suggested a possible role of adipose stem cell (ADSC) in preventing penile tunica albuginea fibrosis in a rat model of acute PD [1]. On the other hand there is a void in the existing literature on whether ADSC treatment is efficacious in reversing fibrosis once a plaque has been established [7]. This aspect is of utmost importance for the translational point of view as the majority of patients presents with an established plaque [5]. In addition, it is worth to remember that there are several issues tied to the use of culture-expanded ADSC such as potential contamination, genetic instability and oncogenesis [8].

Adipose SVF is isolated as part of the aqueous fraction derived from enzymatic digestion of fat tissue [9]. SVF is a heterogeneous cell fraction including endothelial cells, smooth muscle cells, macrophages, regulatory T-cells, fibroblasts, and a large population of stem cells [10]. Several studies have explored the efficacy of adipose SVF in fibrotic diseases with positive outcome [11–13]. Interestingly, in animal models of erectile dysfunction [14] and incontinence [15], SVF treatment showed positive results and efficacy comparable to culture-expanded ADSC. More important, unlike ADSC, SVF is autologous, much more easily acquired, without the need for any cell separation or culturing conditions, and can be performed within a 1.5 h time-frame in a closed system thus limiting the risk of contamination and making it relatively safe [16].

The rat is most commonly animal model for PD due to the analogous morphological and biological penile characteristics with humans. In addition, this animal model presents with low costs for purchase and maintenance. More important, Bivalacqua et al. showed that injection of the TGFb1 in penile rat induced PD-like changes including erectile dysfunction [17].

In our recent study we showed that SVF are able to prevent TA fibrosis formation in a rat model of early phase of PD [18]. In the current study, we investigated the antifibrotic effects of a local injection of SVF after establishment of TA fibrosis in a validated rat PD model.

Methods

Ethical approval

All experiments on animal tissues were approved by the ethics committee of University of Leuven (P 272/2014).

We calculated a sample size of 18 considering 3 groups (6 animals for each group), a statistical power of 0.9, effect size d: 2, alpha level 0.05 (G*Power 3.1).

Animals

Male Sprague-Dawley rats ($n = 18$; 12 wk. old; 300–350 g; Charles River Laboratories, Wilmington, MA, USA) were used. Rats were housed in pairs under 12-h reversed cycle lighting with ad libitum access to food and water. Intraperitoneal ketamine (75 mg/kg) and xylazine (50 mg/kg) were used for anaesthesia for the surgical procedure. Amoxicillin (50 mg/kg intraperitoneally) was administered 1 h prior to the surgical procedures as prophylaxis. Rats were euthanized using carbon dioxide asphyxia.

Isolation of SVF

Animals underwent resection of the para-testicular adipose tissue through abdominal midline incision as previously described [19]. The adipose tissue was rinsed with PBS, minced into small pieces, and then incubated in a solution containing 0.075% collagenase type IA (Sigma-Aldrich, St. Louis, MO, USA) for 1 h at 37 °C with vigorous shake for 15 s in 20-min intervals. The top lipid layer was removed, and the remaining liquid portion was centrifuged at $1000 \times g$ for 10 min at room temperature. The cells were then washed, centrifuged, and the pellet was resuspended in saline. The nucleated cells from the pellet were counted and diluted to 5000 cells per µl in saline, of which 200 µl were kept on ice until injection [19].

Study design

Rats were not-randomly divided into 3 equal groups. The sham group ($n = 6$) underwent injection of 50-µl vehicle (citrate buffer) in the dorsomedial aspect of the right midshaft TA with a microliter syringe after opening the Buck's fascia as previously described. The remaining 12 animals were injected with recombinant 0.5 µg of transforming growth factor (TGF)- β1 in 50-µl vehicle [20]. After 1 month, all rats underwent to resection of the para-testicular adipose tissue and received a second identical TA injection with either phosphate buffered saline (PBS; sham and PD group) or autologous SVF in PBS (1 million cells in 200 µl) (PD-SVF group). Four weeks after the second treatment, 6 rats per group underwent in vivo erectile function evaluation after which the animals were euthanized, and the penises harvested for histological analysis and for protein extraction.

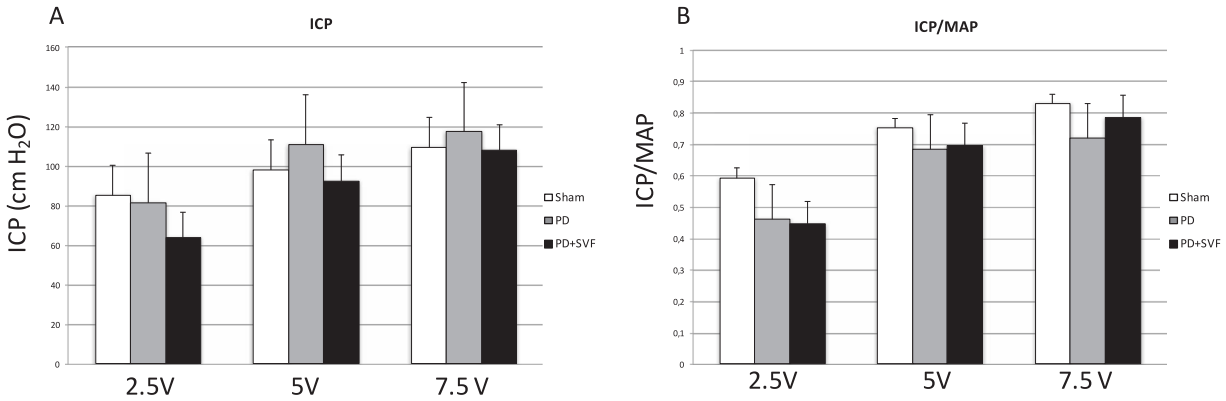

Fig. 1 Erectile function measurement: Summarized data comparing erectile function measurements in sham PD rats and rats treated with PD-SVF at various voltages during cavernous nerve electrostimulation. **a** Intracavernous pressure (ICP). **b** ICP normalized over mean arterial pressure (MAP). +p < 0.05 versus both SHAM and PD-SVF in analysis of variance with post hoc Student-Newman-Keuls analysis

Erectile function measurement

Intracavernous pressure (ICP) response to electrostimulation of the cavernous nerve (CN) was used to evaluate erectile function [20]. Briefly, under anaesthesia, the right CN was exposed and the right crus of the corpus cavernosum was identified and cannulated with a heparinized (200 U/ml) 25-G needle connected to a pressure transducer. The CN was activated (2.5, 5, and 7.5 V) by platinum electrodes connected to a stimulator at 20 Hz for 60 s. The nerve was stimulated once per voltage, and a resting period of 2 min was allowed for nerve recovery between stimulations. Mean arterial pressure (MAP) was recorded by carotid artery cannulation.

Histological analysis of tissue

The penile midshaft at the level of the injection site was harvested, fixed, and further processed for histology. Haematoxylin and eosin and Masson's trichrome staining procedures were performed according to a standard protocol previously described [21].

Western blot analysis

Western blot was performed as previously described [21–23] for the detection of collagen I, collagen III, and elastin proteins at the level of the penile midshaft. Glyceraldehyde-3-phosphate dehydrogenase or Beta-Actin were used as an internal standard. Primary antibodies were Rb Anti-Collagen III (Abcam Inc., Cambridge, MA, USA), Ms Anti-Elastin (1:500, Abcam Inc., Cambridge, MA, USA) and Rb controls against Beta-actin (B-actin) (1: 1000 Abcam Inc., Cambridge, MA, USA), Rb Anti-Collagen I (1:500; Abcam Inc., Cambridge, MA, USA) [22].

Statistical analysis

The results were analysed using Prism v.4 (GraphPad Software, San Diego, CA, USA) and expressed as mean standard deviation of the mean. Multiple groups were compared using one-way analysis of variance followed by the Student-Newman-Keuls test for posthoc comparisons. Statistical significance was set at $p < 0.05$.

Results

No animals died during the experiment. No Major complication happened.

Erectile function

No significant difference was noted in ICP and ICP/MAP values between the three groups at 2.5, 5 and 7.5 volts ($p >$ 0.05 for all voltages) 4 weeks after vehicle or SVF injection (Fig. 1).

Histological and western blot analysis

Rats injected with TGF- β1 (PD group) displayed a minimal deposition of amorphic matrix and a haphazard organization of collagen fibers in the TA which did not extend into the subtunical corpus cavernosum (Fig. 2). These morphologic results were corroborated by quantitative Western blot analysis, which revealed an increased protein content of collagen III and elastin compared to the sham group ($p < 0.05$ for both) (Fig. 3). In the SVF group, the overall structure of the TA and collagen III expression of the penile shafts were comparable to those of sham rats (Fig. 3). Collagen I/III ratio was higher in PD-SFV group comparing with the PD group (p: 0.02) (Fig. 3). Penile

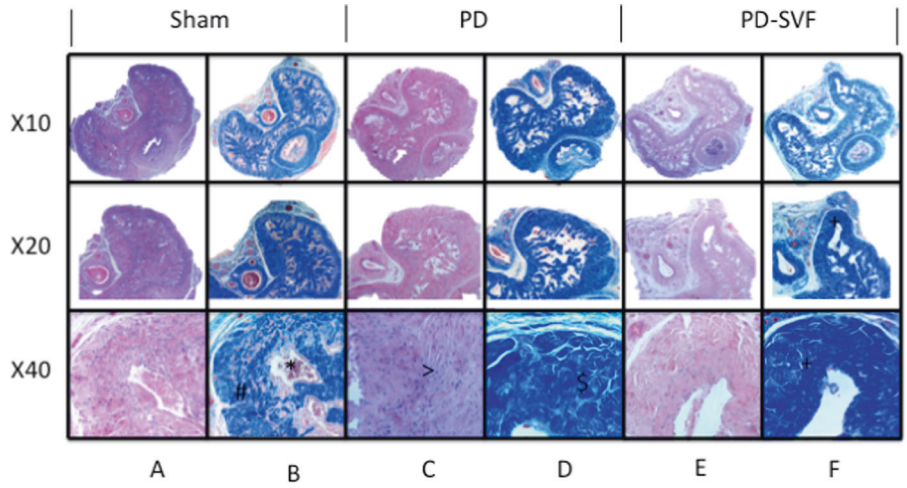

Fig. 2 Histology: Representative photomicrographs of Masson's trichrome and hematoxylin and eosin (H & E) staining in midshaft sections of rat penises at magnification ×10, ×20, and ×40. **a** H & E staining on sections from a Sham rat and (**b**) corresponding Masson's trichrome staining on an adjacent section from the same rat. **c** H & E on sections from a PD rat and (**d**) corresponding. Masson's trichrome staining on an adjacent section from the same rat. **e** H & E sections from PD-SVF rat and (**f**) corresponding Masson's trichrome staining on an adjacent section from the same rat. Note the open cavernous sinusoids in the sham rats (*) and the surrounding normal bilayered structure of the tunica albuginea (#). In PD rats, there is deposition of amorphic extracellular matrix material ($) with scattered high numbers of cells (>), which are expected to be fibroblasts based on their spindle-shaped morphology and relationship with the extracellular matrix. In PD-SVF RAT, there is an increase in extracellular matrix deposition (+); however, collagen fibers seem better organized and sinusoid structure is largely preserved

shafts from SVF-treated rats showed no significant differences in elastin expression compared to the sham and PD ($p > 0.05$). No significant differences in collagen I expression were noted between the three groups.

Discussion

The French Surgeon Francois de la Peyronie (1678–1747) first described PD describing the a series of patients with "rosary beads of scar tissue" [24]. PD is a relatively unknown condition, although recent studies suggest that it may occur in up to 9% of the male population [25]. Because of its impact on male sexual health, it can result in severe physical and psychological morbidity;[5] men may develop penile pain and curvature that may preclude sexual intercourse and reduce pleasure, with detrimental impacts on partner relationships. The pathology of the PD plaque has been investigated by several in vivo and in vitro studies. According to the available information, it is clear that fibrosis is the principal pathological component, combined with fibrin accumulation and different of inflammation degrees [1, 26–28].

The development of PD consists of an active and a chronic phase [5]. Compromised balance of the inflammatory factor production during the active phase causes abnormal wound healing, which in the chronic phase of PD results in collagen-elastin deposits and calcifications [1].

Fibrosis has been considered an inactive process, precluding organ regeneration [1, 29]. However, in the last few decades, this perception has changed. Today, it is clear that fibrosis is not static nor irreversible, but instead the consequence of an incessant remodelling that makes it subject to therapeutic intervention [1]. The most important challenge in fibrosis is to halt fibrogenesis and reverse established fibrosis without delaying wound healing process. Consequently, our increased understanding of fibrosis, its dynamics, and the potential of fibrotic microenvironments to reverse holds promise for the development of highly specific antifibrotic therapies. Stem cells (SCs) have been well known for their ability to differentiate to several types of cell populations [30, 31]. However, this ability is not the only feature that makes these cells appealing for therapeutic application. The secretions of a broad range of paracrine factors by SCs includes growth factors, cytokines, chemokines and even functional small RNAs via extracellular vesicles, which allow these cells to influence and modify their host environment, especially during, and early after injury to the tissue [1, 30, 31]. In recognition of these unique properties, there is an increasing body of evidence for the role of SCs as potential treatment strategy to alleviate fibrosis [2, 4, 29, 32]. In particular, mesenchymal stem cells (MSC) and SVF have been a popular SC type in this context [1].

Although the exact MSC anti-fibrotic mechanisms remain to be clarified, the principal theory is that they act as

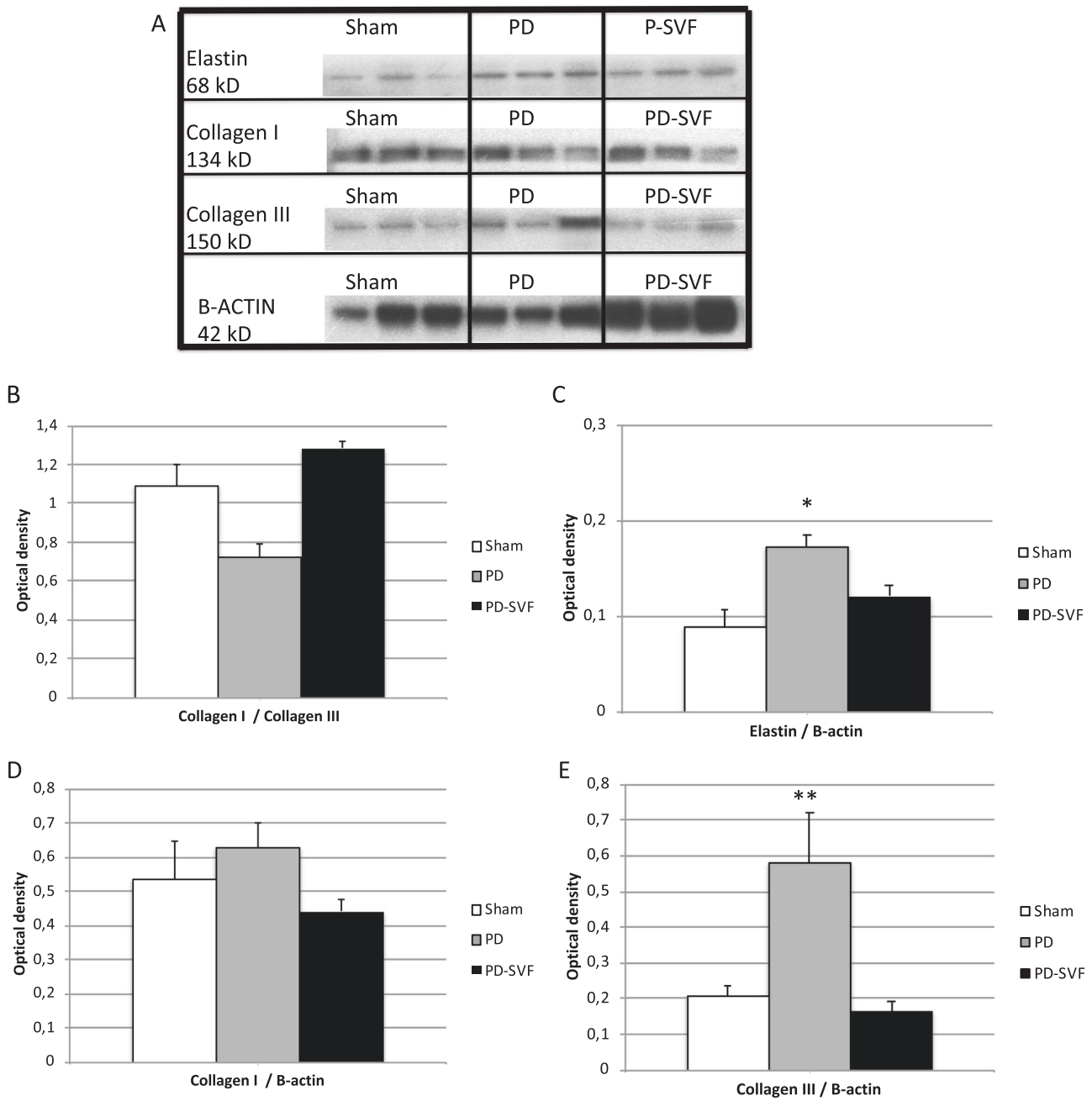

Fig. 3 Western blot analysis for collagen III, Collagen I and elastin. **a** Representative chemiluminescence images of blotted membranes containing protein extracts of all three groups. Double bands are due to binding of antibodies to glycosylated and nonglycosylated forms of these molecules. **b** Collagen I and III expression ratio $^{**}p < 0.05$ versus both Sham and PD-SVF in analysis of variance with post hoc Student-Newman-Keuls analysis. **c** Summarized protein expression levels for elastin $^{*}p < 0.05$ versus Sham in analysis of variance with post hoc Student-Newman-Keuls analysis. **d** Summarized protein expression levels for Collagen I versus both PD-SVF and Sham in analysis of variance with post hoc Student-Newman-Keuls analysis. **e** Summarized protein expression levels for Collagen III $^{**}p < 0.05$ versus both Sham and PD-SVF in analysis of variance with post hoc Student-Newman-Keuls analysis

a "drug-store", affecting several pro-fibrotic factors simultaneously [33]. Most preclinical studies showed that MSCs act through immunomodulation [1]. Another postulated mechanism is the induction of pro-fibrotic phenotypical changes in host fibroblasts, myofibroblasts and smooth muscle cells [34]. Nonetheless, definitive responses are not yet available, and further studies focusing on the mechanisms of action are ongoing.

Our results provide novel evidence that autologous adipose SVF reduces collagen III in a rat model of chronic PD.

To date, 5 preclinical studies [18, 20, 35–37], using the TGF-β1 PD rat model, have evaluated the efficacy of locally

TA ADSC injection. In two of our previous studies, we showed that in the acute PD phase, local injection of human ADSC (hADSC) or SVF prevents the collagen III and Elastin TA accumulation [18, 20]. In these studies, we injected the hADSC or autologous SVF 1 day after the TGF-β1 treatment aiming to mimic the early phase of the disease [18, 20]. Our results were in line with the two preclinical studies performed by Gokce et al [36, 37]. Both these studies showed that TA injection of ADSCs was able to prevent rat TA fibrosis induced by TGF-β1. Despite the promising results of these studies [20, 36, 37], it is known that only a small portion of PD patients present in the early phase of the disease. For this reason, we explored, in another our recent preclinical study, the efficacy of hADSC in a rat model of chronic PD [35]. In this study [35], we injected the hADSC 1 month from TGF-β1 injection. 6 days following injection of TGF-β1, the PD rat showed on histological analysis, less fibrosis than detected after 1 month in the previous study [22]. Furthermore, there was no corpora cavernosa fibrosis and erectile function impairment in the PD group compared with the sham rats. hADSC therapy was able to reduce the expression of TA collagen III but had no effect on collagen I and elastin expression [35].

In the current study, we aimed to assess the efficacy of SVF in the chronic phase of PD using the same animal model and the same study design of our previous experiment [35].

In chronic PD rat, no clear fibrotic plaques were detected on histological analysis. This results were confirmed by our previous study using the same animal model [35]. These data demonstrate that the fibrotic plaques in the TA tend to partially regress spontaneously after 60 days in the TGF-β1 rat model of PD, which clearly is a limitation of the used animal model. Furthermore, in contrast to the previous study using the acute model of PD [22], we did not detect any significant corporal fibrosis. This may explain the lack of erectile function impairment in the PD group compared with the sham rats. These data were in contrast with the results of Gokce et al [36, 37]. In these studies, the PD animals showed erectile dysfunction and the presence of clear TA fibrotic plaque after 45 days the injection of TGF-β. In the present study, we show that late SVF therapy is able to reduce the expression of collagen III but has no effect on the collagen I and elastin expression with a significant change in Collage I/III ratio. Type III collagen is a fibrillar collagen and it is secreted by fibroblasts and other mesenchymal cell types. It is secreted mainly during the wound healing process and it is one of the major players in several inflammation-related diseases such as lung injury, liver and renal fibrosis [4, 38, 39]. In the ECM, type III collagen constitutes the major part of the interstitial matrix together with type I collagen with a type I/III ratio of 2:1 [40]. During the early phase of wound healing, the type III collagen, act as a scaffold for fibroblast attachment. As consequence, initial granulation tissue contains mostly type III collagen and only a minor quantity of collagen I [41]. As wound healing progresses, this ratio is changed, leading to a type I/III ratio of 1:2 [2, 4, 40]. The change in immature type III collagen may result in loss of tensile strength [40]. This shift is detected in many disorders such hypertrophic scars due to an amplified expression of type III pro-collagen mRNA [40]. Based on our study, SVF can restore the normal Collagen I/III ratio in an established TA fibrosis.

This study has inherent limitations including a lack of characterization of the injected cell types. However, others studies, using a similar isolation protocol, have examined the exact composition of SVF [9, 42–45]. More importantly, the evidence that the fibrotic plaques of TA tend to partially regress spontaneously after 60 days represents an important limit of the animal model which has been underreported in the literature.

Conclusion

Local injection of SVF in a rat model of chronic PD significantly decreased collagen III concentration in the TA. Further animal and clinical studies are needed to confirm the promising translational potential of this treatment strategy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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