Erectile Dysfunction

Novel Therapies for an Old Problem

ANOVA

Institute for Regenerative Medicine

Dear reader,

Erectile Dysfunction (ED), which is also known as impotence, is a type of sexual dysfunction which affects most men at some point during their lifetime. It is characterised by the inability to develop and/or maintain an erection of the penis during sexual activity.

Erectile Dysfunction can have significant psychological consequences, as it can burden relationships and result in a negative self-image. With increasing life expectancy an increasing number of men is affected by ED.

Although drugs such as Viagra and Cialis have alleviated the problem, they are far from perfect cures for the patho-physiology of ED.

In this brochure we explain the physiology behind erectile function and dysfunction and provide an overview of novel therapies for ED.

We present the latest therapeutic approaches, particularly the novel opportunities afforded by cellular medicine concerning metabolic and functional aspects.

We hope to welcome you soon in our clinic.

Dr. mult. Michael K. Stehling
Prof. Dr. med. Johannes Atta

Erectile Dysfunction – a Common Problem

Erectile Dysfunction (ED) is a problem which affects approx. 50% of all men between the ages of 40 and 70 years[1]. ED is defined as the inability to have an erection of the penis that is sufficient for sexual intercourse[2].

In about 80% of cases, a physical cause can be identified[3], including cardiovascular disease, diabetes mellitus, drug side effects and neurological problems that may occur after surgical removal of the prostate or similar procedures. Physicians speak of psychological impotence when an erection or penetration is impossible or impaired due to thoughts or feelings; this problem occurs in approx. 10% of all ED cases.

Whilst many men afflicted with ED nowadays profit from treatment with PDE5i (phosphodiesterase type-5 inhibitors)-based medication such as Viagra or Cialis[4], these drugs can cause unpleasant side effects, are contraindicated in some patients[5] and do not always provide the desired results.

Other treatments for ED include injections into the penis or the urethra, vacuum erection devices, and penile prosthesis implantation. These options are considered undesirable by most men because of their invasiveness, artificiality and unsatisfactory outcomes[6].

All of these methods solely treat the symptoms of ED but do not cure the underlying disease process. This might now change with the availability of stem cell-based therapies[7].

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[4] Lue, Tom F., and Keith L. Lee. "Pharmacotherapy for erectile dysfunction." CHINESE MEDICAL JOURNAL-BEIJING-ENGLISH EDITION- 113.4 (2000): 291-298.

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[5] Alwaal, Amjad, et al. "Prospects of stem cell treatment in benign urological diseases." Korean journal of urology 56.4 (2015): 257-265.

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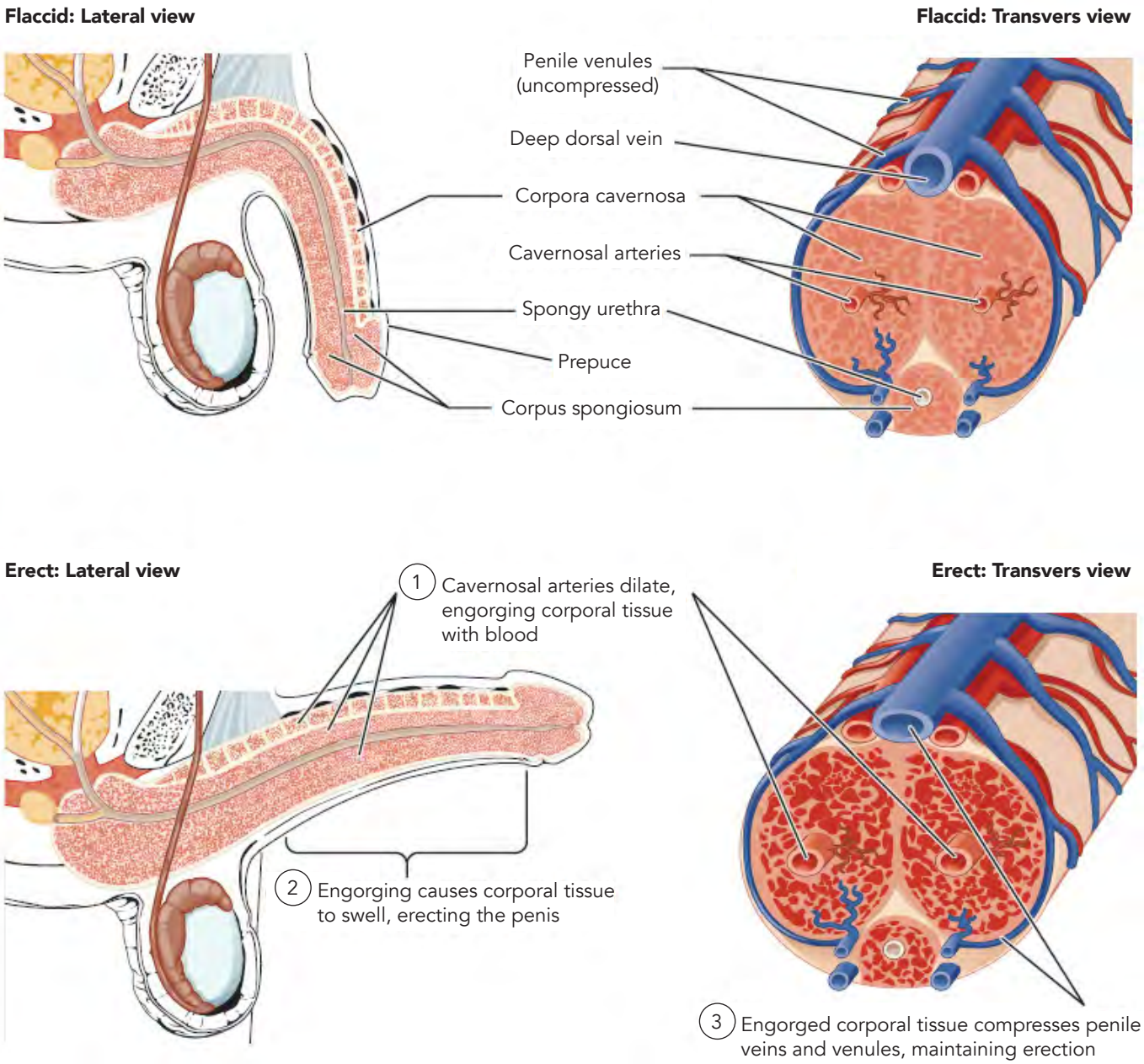

Physiology of Erection and Causes of Erectile Dysfunction

Erection of the penis is effected by filling of the erectile bodies of the penis[8] with blood. Triggered by psychological stimuli, nerve signals from the brain are sent via the spinal cord to the peripheral nerves, which then release nitric oxide (NO) in the erectile bodies. NO causes the smooth muscles of the erectile bodies to relax via the release of cGMP (cyclic guanosine monophosphate), and to engorge with blood. This is the trigger phase of an erection which requires the nerves to function normally.

The enlargement of the erectile bodies in turn compresses the draining veins, between the erectile bodies and the tunica albuginea of the penis, resulting in occlusion of venous outflow and full erection[9]. This is the mechanical phase of an erection.

Detumescence of the penis occurs when cGMP is degraded by an enzyme, called type 5 phosphodiesterase, leading to contraction of the smooth muscles of the erectile bodies, which results in decreased inflow of blood, a consequent reduction in the size of the erectile bodies and a de-compression of the veins, effecting the drainage of blood from the erectile bodies[10].

The key components of an erection are the endothelial cells (EC) and the smooth muscle cells of the erectile bodies, the corpora cavernosa (CSMC), and the release of NO from the cavernosal nerves (CN)[11]. Ageing and a variety of diseases can alter these essential anatomical and physiological components, resulting in ED.

After radical prostatectomy (RPE), the standard treatment for prostate cancer, the CN can be damaged[12]. Whilst the immediately resulting neurogenic ED might be reversible, the long-term consequences, such as diminished NO production, and death of CSMC can lead to atrophy and fibrosis of the erectile bodies, which might result in permanent ED[13,14].
High blood glucose levels in diabetes mellitus[15,16] and increased blood cholesterol and hyperlipidemia[17] can also cause ED by similar mechanisms.

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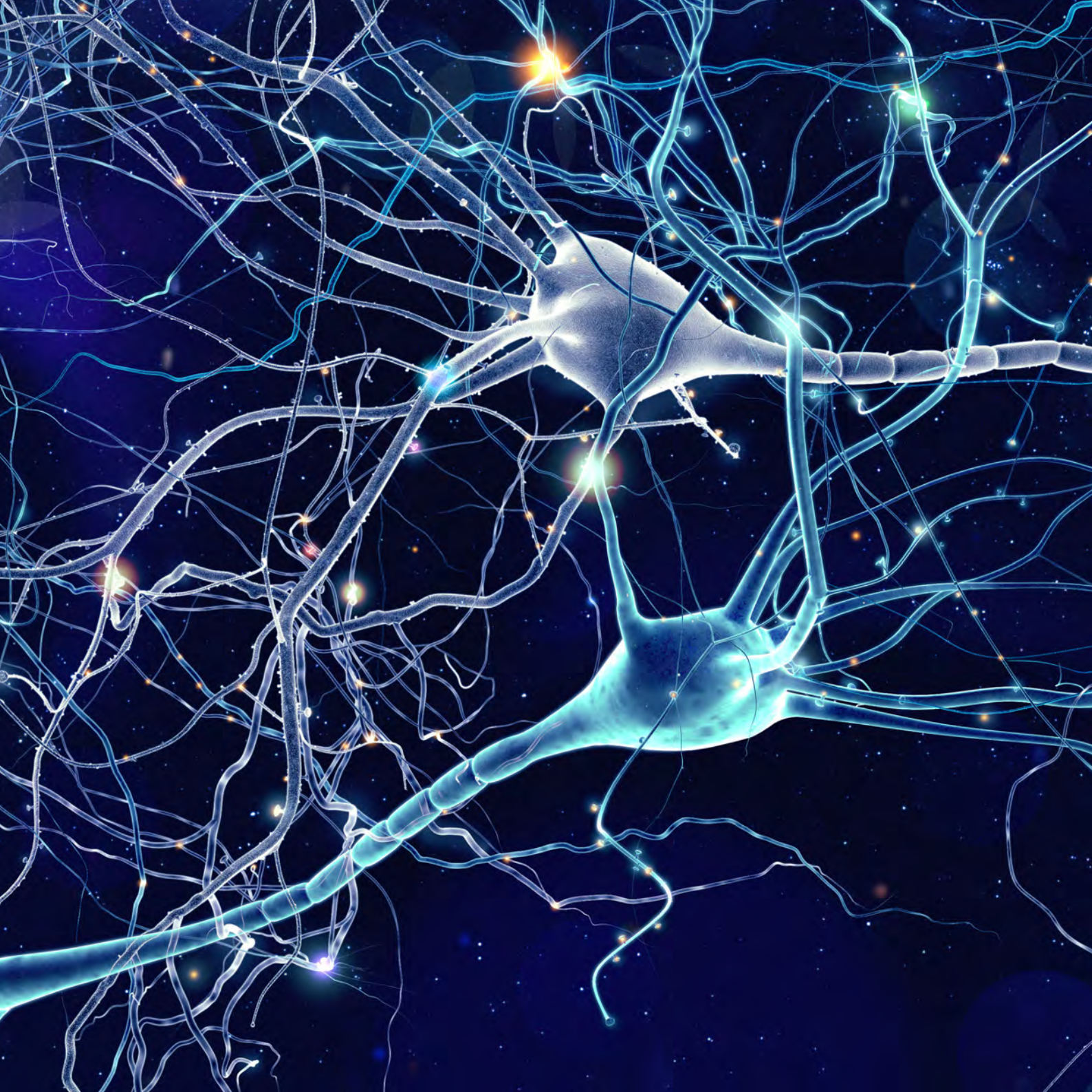

The Role of Stem Cells in the Treatment of Erectile Dysfunction

Stem cells are known to have anti-inflammatory, restorative, and immunomodulatory qualities. They have been effectively tested for the treatment of a variety of pathological conditions, including cardiovascular[18] and neurologic diseases such as stroke[19], spinal cord injuries[20], and Parkinson's disease[21]. Positive effects have also been shown in autoimmune diseases such as multiple sclerosis[22] and systemic lupus erythematosus[23], as well as the healing of wounds[24] and the repair of cartilage defects[25] in osteoarthritis.

Over the past few years, particular enthusiasm has developed for Stem Cell-based Therapies in the urological field, especially for the treatment of Erectile Dysfunction[26].

Several preclinical studies have researched the application of stem cells for urological conditions, particularly Bone Marrow Stem Cells (BMSC) and Adipose-Derived Stem Cells (ADSCs) for the treatment of ED in animal models, summarised by Soebadi et al.[27] in 2016.

In cases of acute ED, the mechanism of repair effected by stem cells is assumed to work on a paracrine level[28]. In chronic ED, however, the effect of stem cells may be mainly based on engraftment and cellular differentiation[27]. The exact mechanism of how stem cells improve erectile function in chronic ED is still not fully clarified[29].

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Publication (year)	No. of men	Cause of ED	Treatment	Assessment	Results
Bahk (2010) Korea	7	Diabetes	Umbilical blood Stem Cells	IIEF-5, SEP, GAQ	Improved rigidity in 2/7, able to penetrate with PDE5i
Levy (2016) France	8	Organic	Placental-Derived Stem Cells	GAQ PSV, IIEF-5	to penetrate with PDE5i 3/8 improved erection; IIEF
Haahr (2016) Denmark	17	5-18 months after RPE	Adipose-Derived Stem Cells	IIEF-5	change not significant 8/11 continent men and 0/6 incontinent men recovered erection
Yiou (2016) France	12	22 months after RPE	Bone Marrow Mononuclear Cells	IIEF-5, EHS, color doppler ultra-sound	1/12 hard erection; 9/12 needed ICI, PDE5i, or VCD. Improved EHS and IIEF-5

Table 1: Results from clinical trials on Stem Cell Therapy for ED.

RPE: Radical Prostatectomy
ED: Erectile Dysfunction
SC: Stem Cell
IIEF-5: International Index of Erectile Function
SEP: Sexual Encounter Profile
GAQ: Global Assessment Question
PSV: Peak Systolic Velocity
EHS: Erectile Hardness Score
PDE5i: Phosphodiesterase type 5 inhibitor
ICI: Intra-Cavernous Injection
VCD: Vacuum Constriction Device

Results from Clinical Trials Prove Effectiveness of Stem Cell Therapy for ED

There are different possible methods of application. The intravenous injection of ADSCs has been shown to improve erectile function [30]. Injection of stem cells into the erectile bodies of the penis (intracorporal) has also been applied, since it is both easy and appears logical [31]. Peri-prostatic injection, with or without a concurrent intracorporal injection, has also been performed [32,33]. All of these applications can potentially help, as the regenerative effect of stem cells is mainly achieved either indirectly by secreting growth factors locally via paracrine mechanisms or by direct migration of the cells to the major pelvic ganglia [34].

The safety, efficacy, and the mechanisms of both Bone Marrow (BM) and Adipose Tissue-Derived (ADSC) Stem Cells for the treatment of ED have been amply evaluated in several preclinical trials. A research group has summarised the data [27]. Almost all of the studies reported improved erectile function in various animal models of CN injury, vascular insufficiency, diabetes mellitus, hyperlipidemia, and ageing.

Whilst concerns about the possible promotion of malignant tumours remain whenever stem cells are being transplanted [35], the use of cell-free solutions of the Stem Cell Secretome, the collection of paracrine factors with which stem cells effect repair, has solved this problem, since it avoids the transplantation of the actual stem cells.

[30] Qiu, Xuefeng, et al. "Effects of intravenous injection of adipose-derived stem cells in a rat model of radiation therapy induced erectile dysfunction." The journal of sexual medicine 9.7 (2012): 1834-1841.

[31] Alwaal, Amjad, et al. "Prospects of stem cell treatment in benign urological diseases." Korean journal of urology 56.4 (2015): 257-265.

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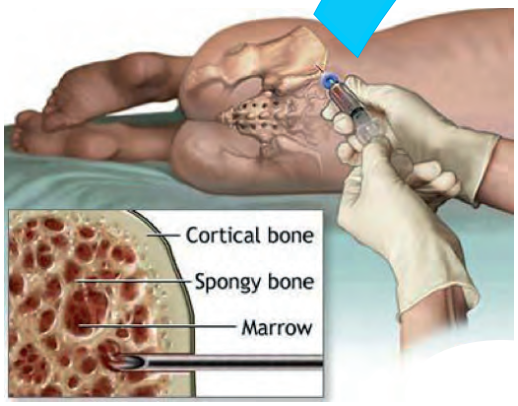
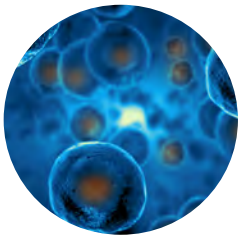
1. HARVESTING OF BONE MARROW

- Minimally invasive procedure
- Natural cells from your own body

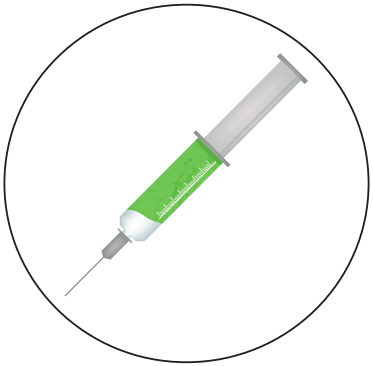


2. PRODUCTION OF THE STEM CELL THERAPEUTIC



- High concentration of haematopoietic and Mesenchymal Stem Cells
- Quality and safety approved by our German lab in compliance with German and European law

TOTAL TIME = 2-3 HOURS



3. APPLICATION OF THE STEM CELL THERAPY

- Intraveneous application
- Safe, fast and effective
- Stimulation of regenerative processes in your body

ANOVA's Comprehensive Treatment Programmes for ED

Stem Cell Therapy is rapidly developing into an effective and safe treatment for ED. To obtain best results, however, Stem Cell Therapy has to be integrated into a comprehensive treatment programme for ED, which addresses all aspects of the condition, such as neurological, vascular, metabolic, endocrine and psychological factors, which can play a significant role in the aetiology of ED.

At ANOVA, our experts in Andrology and Sexual Medicine are uniquely qualified to address all of these issues to ensure optimal outcomes:

- Prescription of medication to improve, optimise and maintain erectile function
- Endocrinological analysis and hormone supplementation
- Metabolic testing and optimisation
- Choice of natural food supplements to support optimal sexual function
- Individual sports, exercise and physiotherapy programmes for healthy urogenital function
- Application of pulsed ultrasound for improved erectile function
- Demonstration of supportive devices for induction and maintenance of erection
- Counselling concerning penile surgery and implants

Our medical professionals, a team of dedicated physicians, patient care managers and scientists, are ready to provide you with the high quality medical care that you deserve.

ANOVA Scientific and Medical Advisory Board

We believe that an ideal treatment of any kind is based on the individual's needs and concerns. To be able to meet such high standards, a detailed diagnostic work-up is necessary.

At ANOVA Institute for Regenerative Medicine we offer full diagnostic work-ups with state-of-the-art technology, innovative laboratory diagnostics and the knowledge of trained and specialised physicians who will meet your needs.

With our potent Stem Cell Products, the Bone Marrow Concentrate and next generation Stem Cell Secretome, we can provide you with novel and innovative cellular therapy.

Enhancing the Effect of Stem Cell Therapy with Prostaglandins

Prostaglandins are a group of physiologically active lipids called eicosanoids. They have many hormone-like effects, and type PGE1 can help with physiological functions linked to ED, such as vasodilatation of blood vessels in erectile tissues of the corpora cavernosa. They can also increase cavernosal artery blood flow, which is necessary for penile rigidity.

After its application, the onset of erection is within 5 to 30 minutes. The drug has a short half-life in men and improvement of erections may last from 1 to 2 hours.

The drug is applied to the tip of the penis and is available in two dosage strengths. It can be used as needed to achieve an erection.

Our expert physicians will guide you through the process in a consultation on-site.

The Effects of Testosterone

SKIN

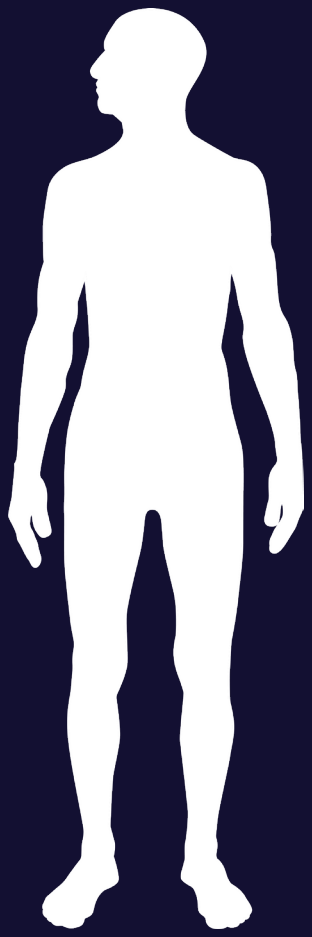
Hair growth
Collagen growth

MUSCLES

Muscle growth
Increased strength
Increased endurance

BONES

Bone mass density
maintenance



BRAIN

Increased sex drive
Improved mood
Confidence
Memory function

BONE MARROW

Red blood cell
production

SEX ORGANS

Sperm production
Erectile function

Hypogonadism and Hormone Substitution with Testosterone

Hypogonadism is defined as a reduced functional activity of the gonads — the testes in men or the ovaries in women — which may result in declined production of sex hormones.

A low sex drive can be caused by imbalanced testosterone levels. Testosterone is one of the key players in a man's health and well-being. Many men with low serum testosterone levels have reported improved energy levels, sex drive, erection and mood after testosterone treatment.

There are many forms of Testosterone Replacement Therapy options, including intra-muscular injections and testosterone gel for a daily topical application.

At ANOVA Institute for Regenerative Medicine, we offer individualised treatments for our patients and compile treatment programmes which include all possible medical measures for maximum treatment success. Testosterone Replacement Therapy in combination with Stem Cell Therapy can be the most effective approach to improve your erectile function.

ANOVA's Comprehensive Treatment Programmes for ED:

Stem Cell Therapy is rapidly developing into an effective and safe treatment for ED. To obtain best results, however, Stem Cell Therapy has to be integrated into a comprehensive treatment programme for ED, which addresses all aspects of the condition, such as neurological, vascular, metabolic, endocrine and psychological factors, which can play a significant role in the aetiology of ED.

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- Demonstration of supportive devices for induction and maintenance of erection
- Counselling concerning penile surgery and implants

Our medical professionals, a team of dedicated physicians, patient care managers and scientists, are ready to provide you with the high quality medical care that you deserve.

Meet the dedicated team of ANOVA Institute for Regenerative Medicine:
Expert medical professionals and scientists, ready to provide you with the high quality medical care you deserve.

Michael K. Stehling

MD, PhD
Professor of Radiology,
fmr. Clinical Fellow
Harvard Medical School, Boston, USA
fmr. Associate Professor of Radiology
at Boston University, USA.

Johannes Atta

MD
Professor of Haematology,
Specialist in Internal Medicine,
Haematology and Clinical Oncology,
Medical Quality Management.

Contact

ANOVA
Institute for Regenerative Medicine GmbH

Strahlenberger Straße 110
63067 Frankfurt am Main
Offenbach, Germany

Phone: +49 (0) 69 50 50 00 944
Email: info@anova-irm.com
Internet: www.anova-irm.com

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Institute for Regenerative Medicine