SEXUAL MEDICINE REVIEWS REVIEW

Thinking About Pathomechanisms and Current Treatment of Erectile Dysfunction—"The Stanley Beamish Problem." Review, Recommendations, and Proposals

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ABSTRACT

Introduction: Up to 50% of all men over 50 years of age suffer from erectile dysfunction. Since the late 1990s erectile dysfunction has been treated mostly with phosphodiesterase 5 inhibitors (PDE5I). Over the past 20 years, numerous scientific findings on the development of erectile dysfunction have been collected, which have so far received little attention in the treatment of erectile dysfunction.

Objectives: The objectives of this study were to review the existing medical literature on erectile dysfunction regarding physiology, pathophysiology, and especially therapeutic options beyond treatment with PDE5I and to enable a more effective and especially sustainable treatment for erectile dysfunction.

Methods: A literature review was performed by using PubMed from 1985 to 2020 regarding the physiology, pathophysiology, and treatment of erectile dysfunction.

Results: Since the end of the 1990s an enormous amount of knowledge has been gained about the physiology/pathophysiology of erection/erectile dysfunction. Based on these findings, numerous physical, drug, and holistic therapeutic options (beyond the application of PDE5I) have been developed for the treatment of erectile dysfunction. However, these are still relatively rarely used in the therapeutic concept of erectile dysfunction today.

Conclusion: Based on scientific findings of the last 20 years, there are numerous therapeutic approaches, including lifestyle modification, specific pelvic floor exercises, shock wave treatment, and the application of different supplements. The long-term treatment of erectile dysfunction should now go beyond the purely symptomatic use of PDE5I. **W-D Beecken, M Kersting, W Kunert, et al. Thinking About Pathomechanisms and Current Treatment of Erectile Dysfunction—"The Stanley Beamish Problem." Review, Recommendations, and Proposals. Sex Med Rev 2020;XX:XXX–XXX.**

Key Words: Erectile Dysfunction; Physiology; Pathophysiology; Treatment Concepts

INTRODUCTION

In 1967 the television series "Mr Terrific" was broadcast on American television for the first time. In terms of content, it was about a rather slender, shy, and somewhat dull protagonist (Stanley Beamish), who at times gains superpowers by taking a pill. Through the pill Beamish develops supernatural powers and gains self-confidence, but despite all his heroic actions the somewhat nerdy character remains. When the pill loses its effect (after 1 hour), Beamish transforms back into his original personality.

In an amazing way, the drug-induced transformation of this serial character is reminiscent of the effect of drug therapy on patients with erectile dysfunction. If the affected patients achieve an erection capable of sexual intercourse for a short time, this gained effect fades away without improving the overall situation of the patient or achieving a long-term recovery. This symptomatic treatment of erectile dysfunction, which is currently

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carried out almost exclusively on the basis of the use of phosphodiesterase 5 inhibitors (PDE5I), does not take into account the scientific knowledge of the causes and treatment options for erectile dysfunction over the last 20 years. We refer to this fact as the "Stanley Beamish Problem."

Fatally, the possibility of the simple and symptomatically effective treatment of erectile dysfunction with a "pill" has led to a frequently unreflective prescription without diagnostic clarification of the underlying causes. Therefore, underlying findings that trigger and intensify erectile dysfunction are not identified and also not addressed therapeutically. Associated with this procedure is a creeping further development of the underlying disease, a reduced effect of the symptomatic drug therapy over time, and the risk of fatal events associated with unrecognized secondary disease.

Drug treatment with PDE5I is by far the most common first-line therapy for patients with erectile dysfunction.[1] Different therapeutic regimens, such as on-demand or continuous application of the various active drugs, have become widely established. In particular, the continuous administration of tadalafil over many months was expected to have a curative effect over time. Unfortunately, a curative effect could never be shown in scientific studies.[2] Combination therapies with tadalafil and additional active ingredients (such as L-arginine) have in some studies produced a slightly better effect, but not a lasting one.[3] In this respect, treatment of erectile dysfunction with PDE5I is purely symptomatic treatment. Patients acquire, comparable to Stanley Beamish, for a short time a "supernatural" ability which they can use more or less effectively (the ability to fly acquired by Beamish seems somewhat awkward and bumbling in practice).

Medical treatments should have a curative intention if possible. If curative treatment is not possible due to a lack of existing therapeutic drugs or procedures, by definition a chronic therapy concept (permanent treatment) is aimed at. Many diseases of civilization, such as arterial hypertension or diabetes mellitus, are considered chronic diseases and are treated with chronic therapeutic concepts. Chronic therapy concepts aim to alleviate symptoms and, if possible, to slow down the progression of the underlying disease and prevent adverse consequences of the underlying disease. Against this background, when considering erectile dysfunction, it seems particularly important to note that there are certainly underlying causes of this disease which allow for curative treatment (venous leakage, psychological factors). Thus, the diagnosis of the underlying findings of erectile dysfunction has to be a trend-setting aspect for the therapy and should not be neglected. Even the isolated introduction of the purely symptomatic, drug treatment of erectile dysfunction appears questionable in view of the neglected therapeutic aspects of preventing adverse effects of underlying findings and slowing down the progression of the underlying disease. The basic principle of medicine—no therapy before a definite diagnosis—should also be observed and followed in the treatment of erectile dysfunction.

The basis of every therapeutic option is a comprehensive knowledge of the physiology and pathophysiology of the entity to be treated. Therefore, in this review we focus on the physiological-pathophysiological aspects of erection and erectile dysfunction and associate them with possible therapeutic applications that go beyond purely symptomatic drug treatment with PDE5I.

We hope to contribute to a better therapeutic approach to the multifactorial genesis of erectile dysfunction and, in the medium term, to shift the therapy of erectile dysfunction away from a purely symptomatic character toward a more regenerative and perhaps curative approach.

CONSIDERATION OF THE PHYSIOLOGY/ PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION

It has been scientifically shown that the development of erectile dysfunction is a multifactorial process that is associated with conditions like metabolic syndrome, coronary heart disease, diabetes mellitus, hyperlipidemia, hypogonadism, trauma, prostate hyperplasia, depression, and numerous other psychological and physiological states which negatively affect nerve activity, hormone secretion and perception, blood supply and disposal, biochemical processes, and microanatomical structures.[4] The composition of the underlying factors can vary greatly, and the respective leading components can lead to differently structured forms of erectile dysfunction. It is obvious that these differently structured forms of erectile dysfunction require different therapeutic approaches. Therefore, the detailed diagnostic classification of erectile dysfunction (in individual cases) must absolutely precede any therapeutic intervention. A prerequisite for adequate diagnostics is knowledge of the physiology, pathophysiology, and pathogenesis of erection and erectile dysfunction. Therefore, we will shed light on the complex pathogenesis of erectile dysfunction in different levels (genetic, biochemical/molecular, and microanatomical).

Normal erection is based on a meticulous interplay of hormonal, neuronal, and vascular processes, which can be compromised at the genetic, molecular, and microanatomical level.

Erection can be induced in different ways. Central erection (psychogenic) triggered by thoughts, smells, ideas etc finds its origin in the different perception centers of such stimuli, which are integrated in the medial preoptic area of the hypothalamus by the release of oxytocin and dopamine. Different nerve fibers transmit the resulting erection impulse to autonomous and somatic spinal centers, the main erection center being located in the sacral medulla (S2−S4). The fibers that lead down from the brain exert both stimulating and inhibiting activities on the

erection.[5,6] From the sacral erection center (S2−S4), parasympathetic nerve tracts are passed on as nerves belonging to the inferior hypogastric plexus, where they unite with sympathetic nerve fibers. Together they run through the small pelvis as cavernous nerves and finally enter the erectile tissue. In cavernous bodies, cholinergic parasympathetic nerve fibers enter the endothelial cells lining of the vessels and sinusoids, where they release their messenger substance acetylcholine via synapses. The secreted acetylcholine leads to the activation of endothelial nitric oxide synthase (eNOS) in the endothelial cells, which activates nitric oxide (NO) production and releases it to the smooth muscle cells. Non-adrenergic, non-cholinergic (NANC) parasympathetic fibers of the cavernous nerves run directly to the smooth muscle cells of the penile vessels and sinusoids, where they release their messenger substance NO, which is produced in the nerve endings by activated neuronal nitric oxide synthase (nNOS) and vasoactive intestinal peptide via synapses.[6−8] Vasoactive intestinal peptide activates adenylate cyclase in the muscle cells, which catalyzes adenosine triphosphate to cyclic adenosine monophosphate (cAMP). The NO originating from the NANC fibers and from the endothelial cells activates guanylate cyclase for catalysis of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate. cGMP stimulates, via the protein kinase G, a potassium channel which transports K+ out of the cell, inhibits a calcium channel which transports Ca2+ into the cell, and stimulates a calcium channel that transports Ca2+ into the endoplasmic reticulum of the cell. cAMP supports the stimulation of the potassium-transporting channel via protein kinase A. The totality of this ion shift leads to hyperpolarization of the smooth muscle cell and thus to its slackening.[9] In addition to the system mediated by nitric oxide synthetase (NOS) and nitric oxide (NO), there are other regulatory circuits, such as the carbon monoxide/heme oxygenase-1 (HO-1) system, which also mediate the relaxation of smooth muscle cells in the corpora cavernosa.[10]

There is another (reflexive) way of stimulating an erection. In this case the sensory signals reach the sacral medulla via the N. dorsalis penis and the afferent, sensory part of the N. pudendus. There also is a second afferent pathway from the pelvic-perineal region via the hypogastric nerve to a thoracolumbar spinal center. The sensory signals are integrated in the spinal cord and transmitted to the higher centers. After central integration of various aspects, the erectile impulse is transmitted to the sacral erection center, as in the centrally triggered erection, and is then transmitted to the penile functional tissue via the aforementioned nerves. The tactile stimuli can also be switched directly in the sacral erection center and trigger an erection (reflexogenic erection).[6]

Parasympathetic activity generally has an erection promoting effect and sympathetic activity has an erection inhibiting effect, whereby inhibition of the sympathetic-mediated contraction of the smooth vascular muscles also leads to erection promotion. In addition, the sympathetically mediated vascular contraction in areas outside the pelvic vessels can enable an increased blood supply to the penis and thus sympathetic activity also can demonstrate a direct erection supporting effect.

The stimulation of nNOS (in the nerve endings of the NANC fibers) and the associated release of NO into the smooth muscle cells lead to an initial increase in blood flow into the penile sinusoids. This increased blood flow in turn maintains the induction of eNOS by sheared stress on the endothelial cells.[11] The strong and unimpeded (by also flaccid smooth muscles) expansion of the sinusoids leads to increased intravascular pressure in the corpora cavernosa and thus to compression of the draining veins as they pass through the penile fascia (venous occlusive effect).[12]

Erection of the male penis is an extremely important mechanism in evolutionary terms, because without the erection of the penis, reproduction of the species is not possible. Probably because of this importance, nature has introduced a certain redundancy into the development of erection. Thus, for example, in the central process of NO provision, it cannot be assumed that the synthases (eNOS and nNOS) originating from different cell types work in competition. Rather, it can be assumed that this important and central mechanism of erection development works synergistically and/or is substitutionally provided by the different enzymes. Evidence for such a redundancy is provided for example by studies with homozygous nNOS−/− knockout mice, which show completely normal erections and normal sexual behavior.[13] This study proves that the development and maintenance of erection does not essentially depend on the production of NO by nNOS. It could now be argued that the production of NO by nNOS (NANC fibers) may only need to occur for a short period of time to initiate the erection, and that maintenance via eNOS is the longer term and more important factor during the erection process. The short-term NO production by nNOS could be taken over by eNOS or other enzymes (eg, inducible NOS). However, it is true that eNOS does not appear to be essential for erection either, since eNOS−/− knockout mice also show normal erections.[14] Surprisingly, the eNOS−/− knockout mice, which showed normal erections, showed significantly reduced NOS activity (about 40%), as well as significantly reduced NO activity and reduced cGMP production in penile tissue.[14,15] Of particular interest in this observation is that men with erectile dysfunction also show significantly reduced systemic NO activity. This could be an expression of endothelial cell damage underlying the disease. The authors explain why the mice show normal erections despite the significantly reduced NO activity in the penile tissue with a possible reduction of the RhoA/Rho kinase-induced contraction of smooth muscle in the penis.[14] It is not uncommon in physiology for a certain effect to be produced by inhibition of an opposite mechanism.

These complex neuronal-vascular-molecular interactions with intact anatomical-mechanical structures (supplying arteries, elastic sinusoids) can be impaired at various points and lead to

the development of erectile dysfunction. Biochemical processes may be impaired. For example, nerve damage (of varying genesis) can lead to a reduction in cGMP and, as a result, insufficient relaxation of the arterial vascular musculature and the muscle cells of the sinusoids.[16] Since cGMP is also produced and secreted by endothelial cells (eNOS), endothelial cell damage of different etiologies may also prevent adequate muscle relaxation.[17] The impaired relaxation of the musculature of the vessels and sinusoids results in both a reduced inflow of blood into the cavernous bodies and an increased outflow of blood from the sinusoids (venous leakage, venous occlusive disease).[18] In addition, structural changes, such as arteriosclerosis of the penile arteries, or varicose changes in the draining veins of the penis can also lead to the development of erectile dysfunction. Furthermore, different genetic changes, especially in the eNOS, can lead to erectile dysfunction.[19] Finally, there are psychological components of erectile dysfunction with varying degrees of severity, which may be secondary or act as the primary trigger of erectile dysfunction.[20] As already mentioned, it is assumed that erectile dysfunction is multifactorial in origin, which can include all of the above pathomechanisms in parallel or in isolation. Drug therapy with PDE5I leads to a very good symptomatic effect in about 60% of patients (defined as the induction of an erection sufficient for penetration). However, the effect of PDE5I requires at least partially intact neural and endothelial function.[21] To what extent the molecular components of erectile development are responsible for the development of erectile dysfunction is practically difficult to differentiate and will probably vary greatly from case to case. Even the anatomical components that are in the lead (arterial insufficiency, venous leakage, nerve damage, or endothelial damage) cannot be easily identified in individual cases. For example, if erectile dysfunction caused by radical prostatectomy is assumed to be caused by nerve damage, the characteristics of erectile dysfunction after radical prostatectomy can be very different even if the nerves are preserved on both sides. To assume more or less pronounced damage to the nerves as the cause of the more or less impaired erection would not do justice to the complexity of the erection mechanism. It is probably much more obvious to assume a subclinical weakening of the system (in the naturally older patient clientele), which is already present at several points of the erection cascade. Like many other bodily functions, this weakening can be compensated for over a long period of time. However, if a single component (in this case the nerve function) is severely impaired (caused by the operation), the compensatory mechanisms are overtaxed, and the patient shows corresponding clinical symptoms. Conversely, it is conceivable that there are people in whom, for example, the endothelial component of erectile development is significantly more active than, for example, the neuronal component, and therefore damage to the nerves only causes a slight impairment of erectile function. This hypothesis would postulate different types of erection development, which would pose an additional challenge in the differential diagnosis and especially in the differential treatment of erectile dysfunction. In this respect, a specific therapy for erectile dysfunction based on the underlying molecular and anatomical causes will be difficult to plan in advance. However, this complexity and difficulty of the problem should not lead to the use of drug therapy (with PDE5I) as the universal therapeutic approach. On the contrary, if we are not able to identify the respective component composition of erectile dysfunction in an individual case due to a lack of diagnostic possibilities today, a strategy for identification of an optimal therapy must be developed. If one assumes that a multifactorial event, in which individual factors contribute differently to the appearance/development of the clinical picture in the individual case, is treated most effectively by a therapy adapted to the triggering factors, the therapy of erectile dysfunction must follow a multimodal approach. An intelligent therapeutic strategy would have to be based on a tentative treatment adapted to the probability of the developmental components in the individual case. The aim following this strategy is not to be effective with the first treatment regimen, but to identify the optimal therapy for the individual erectile dysfunction in the medium term.

Furthermore, erectile dysfunction often coexists with ischemic heart disease. Ischemic heart disease is the leading cause of morbidity and mortality accounting for millions of deaths globally every year. Vascular erectile dysfunction is an independent risk factor for ischemic heart disease and may precede cardiac symptoms by 3–4 years. The common link is endothelial dysfunction, with both diseases sharing the same etiology, risk factors, and pathogenesis. Endothelial dysfunction and plaque burden in the smaller penile arteries may cause symptoms of erectile dysfunction before they affect the blood flow in the larger coronary arteries. Aggressive risk factor control and lifestyle modification are recommended, which will not only improve symptoms of erectile dysfunction but also reduce cardiovascular risk.[22]

THERAPEUTIC ASPECTS OF ERECTILE DYSFUNCTION

Since the introduction of PDE5I in the treatment of erectile dysfunction in the late 1990s, no drug therapy approaches with a new mode of action have been integrated into therapy. Numerous new therapeutic targets have been identified in recent years and the corresponding mechanisms of action, such as melanocortin receptor agonist, Maxi-K channel activator, guanylate cyclase activator, immunophilins, NO donor, and stem cell therapy have been investigated.[21,23,24] However, at present, the only practical treatments available for patients with erectile dysfunction are PDE5I, traditional local injectable drugs such as alprostadil, natural supplements, and physical therapies such as vacuum pumps and the newer shock wave therapy. We will compile and analyze available data on the frequently used active ingredients and therapeutic methods. The integration of these available treatment options should be investigated further to optimize the treatment of men with erectile dysfunction with what we have in our hands today.

Phosphodiesterase 5 Inhibitors (PDE5I)

As already mentioned, the administration of PDE5I is the most commonly used treatment for erectile dysfunction. The American Urology Association guideline explicitly states that all available treatment options (regardless of their invasiveness or irreversibility) should be presented to the patient and offered as first-line therapy.[25] Since this review focuses on therapeutic options beyond the administration of PDE5I, this form of therapy will not be discussed in detail here. Further information on pharmacotherapy for erectile dysfunction with PDE5I can be found elsewhere.[26] So we will provide some information on the problems with the treatment of erectile dysfunction with PDE5I that make other treatment options necessary. In the primary and undifferentiated prescription of PDE5I, it should be kept in mind that about 40% of patients treated have no primary effect on PDE5I.[27] Since erectile dysfunction is a psychologically stressful event for men, it takes on average 2−3 years for a man affected to see a doctor. If the problem presented by the patient (often at the end of a consultation, as an additional observation) is only briefly acknowledged by the prescription of a PDE5I and this therapeutic attempt then shows no effect, the patient will probably not visit a doctor with those issues again. This means that on one hand, with this undifferentiated therapy, we deny the man concerned the possibility of a more effective therapy, and on the other hand we thwart the discovery of significant findings underlying erectile dysfunction. In this situation, the affected man would be much more helped by referral to an appropriately oriented specialist. Furthermore, numerous studies report an approximately 50% discontinuation rate of PDE5I intake for various reasons (ineffectiveness, adverse events, anxiety).[27] So, it is very well documented that about 10−25% of erectile dysfunction patients experience mild adverse events including headache, flushing, nasal congestion, and dyspepsia while taking PDE5I.[28] In particular, the primary ineffectiveness, adverse events, and the apparent loss of effectiveness in some patients make multifactorial therapy necessary with regard to the triggering components of the disease. We think that with PDE5I we have a very powerful therapeutic agent for erectile dysfunction in our hands. However, the often-good primary therapeutic effect should not obscure the view of possible simpler, cheaper, and equieffective treatments with fewer adverse events, as well as multifactorial therapy (with or without PDE5I) to increase the effect and perhaps better therapeutic compliance. In this respect, we see PDE5I as a valuable agent in the treatment of erectile dysfunction, either as a symptomatic therapeutic agent or as part of an integrated therapeutic concept with a sustainable approach.

Intracavernosal Self-Injection Therapy (ICI)/ Medicated Urethral System for Erection (MUSE)

Another method of treating erectile dysfunction is ICI with various vasoactive substances (alprostadil, papaverine, phentolamine). ICI is widely described as a second-line therapy for erectile dysfunction, as it is also effective when orally administered PDE5I is not effective.[29] This increased efficacy of ICI is due to the direct influence of the cGMP or cAMP-producing enzymes (adenylate cyclase and guanylate cyclase) with the omission of the detour of PDE5I.[29] Approximately one-third of patients in whom both oral administration of PDE5I and ICI lead to an erection capable of sexual intercourse choose to maintain ICI.[30] A slight variation of ICI is the MUSE, where an alprostadil pellet is applied to the urethra. The success rate with MUSE is significantly lower than with ICI. While success rates of >90% are documented for ICI, success rates of only slightly more than 40% are found for the application of MUSE.[31,32]

We see a valuable aspect in the use of ICI/MUSE in the rehabilitation of an erection (e.g. after radical prostatectomy). This rehabilitative effect could be counteracted by erectile tissue fibrosis, described as a side effect of ICI, which, however, appears to occur only after prolonged and, in particular, very frequent use.[29] Other side effects include priapism (about whose possible occurrence and handling the patient must be informed) and occasionally developing penis pain. However, both side effects are rare (<5%) and in the case of penis pain they are usually mild.[29]

Lifestyle Modification

The lasting influence of an unhealthy lifestyle—characterized by cigarette smoking, high alcohol consumption, poor diet, poor sleep quality, and lack of exercise—has been demonstrated in many scientific studies.[33] This fact is also underlined by the association of erectile dysfunction with numerous comorbidities, such as diabetes mellitus, metabolic syndrome, hypertension, and arteriosclerosis, all of which are also associated with an unhealthy lifestyle.[34] Comprehensive meta-analyses demonstrate the positive effects of lifestyle adjustment on erectile function in men.[35,36] The sense and effect of a healthy lifestyle seem to be catchy even for medical laymen. Nevertheless, the greatest challenge of this long-term therapeutic measure lies in maintaining (compliance, adherence) the changed lifestyle.[37] Estimates for general medical patient collectives suggest that 40% of patients do not follow the instructions of their doctors. This figure increases to 70% when significant and complex changes of daily habits are required.[38] On the other hand, retention of lifestyle changes increases when patients understand the purpose behind the intervention and the intervention is relatively easy to implement.[38] In this respect, the transfer of information and knowledge about the disease pattern to be treated and the long-term measures introduced is an essential factor in this therapeutic concept. With regard to the clinical picture of erectile dysfunction, the quick and easy to achieve symptomatic therapy by taking a PDE5I represents an additional problem compared to the long-term effects of a lifestyle change, which requires commitment and perseverance to be achieved. In this respect, intensive information transfer and regular counseling play an essential role in achieving a sustainable therapeutic effect. In an

umbrella review by Allen et al, the data from nearly 4 million patients that performed lifestyle changes (cessation of nicotine use, low alcohol consumption, healthy diet, adequate sleep, stress reduction, and physical activity) showed a clear positive effect on the erectile performance of men with erectile dysfunction.[34,36] The most prominent element of lifestyle change seems to be the termination of a sedentary lifestyle by physical activity.[39,40] Across all erectile dysfunction treatments (including PDE5Is), physical activity often shows the largest improvements in erectile function.[37] However, since initiating and maintaining regular physical activity is a long-term, difficult, and complex lifestyle change, intensive support of these measures through strategic motivation measures is essential.[37] Moreover, lifestyle modification, and in particular physical activity (adapted to individual performance), is an important factor in the treatment of erectile dysfunction and should be communicated and recommended to the patient in all cases.

Physiotherapeutic Exercises

Physical activity has already been described as an important factor to maintain or restore erectile function.[35] However, pelvic floor exercises can provide additional benefits to men by targeting specific areas important for erectile function. This is very well illustrated in an older physiotherapeutic study,[41] in which 55 men with erectile dysfunction were treated either with biofeedback-guided pelvic floor exercises and instructions of lifestyle changes (intervention group) or with instructions of lifestyle changes alone (control group). Compared to the control group, the intervention group showed a significant improvement in the International Index of Erectile Function-Erectile Domain (IIEF-ED) score. This additional effect of pelvic floor exercises was also observed in the control group after pelvic floor exercises were also implemented in these subjects.[41] The pelvic floor, consisting of fasciae, ligaments, and muscles, essentially has 3 functions: (i) support of the abdominal structures, (ii) coordinating the contraction of the anal and urinary sphincters, and (iii) supporting erection and ejaculation.[42] In particular, the bulbospongiosus and ischiocavernosus muscles are considered to be responsible for supporting sexual functions.[41,43] The contraction of the ischiocavernosus muscle leads to a significantly suprasystolic pressure in the corpora cavernosa, which is the basis for a fully developed erection. The contraction of the M. bulbospongiosus causes an increased blood filling and pressure increase in the glans and corpus spongiosum. The effectiveness of erectile control by these muscles depends directly on muscle strength and coordination.[43] Pelvic floor exercises and the associated strengthening of the pelvic floor muscles are effective not only in iatrogenic-induced erectile dysfunction (after radical prostatectomy), but also in erectile dysfunction caused by venous leakage.[41,44] The main focus of most studies on physiotherapy of the male pelvic floor is the preservation or restoration of urinary continence after radical prostatectomy. Also, with regard to the physiotherapeutic effects on erectile function, the majority of the available scientific literature refers to erectile dysfunction following radical prostatectomy. Prota et al showed in a prospective study significantly better erection rates (47% vs 12%) in the treatment group (pelvic floor exercises) compared to the control group (no pelvic floor exercises) after 12 months.[45] In a recent review of the effectiveness of pelvic floor exercises to maintain erection after radical prostatectomy (7 included studies), a clearly positive effect of the interventions in conjunction with biofeedback could be demonstrated in such patients.[46] There are only a manageable number of references to erection promoting pelvic floor exercises as a therapeutic measure in the context of general erectile dysfunction (independent of pelvic surgery). The widespread neglect of pelvic floor exercises as the only effective therapeutic measure for erectile dysfunction is probably essentially based on the significant benefit conferred by one-on-one professionally guided and individualized instruction, the relatively delayed time frame until benefit compared with medication and the (associated) expected poor therapy compliance of the client (comparable to complex lifestyle changes, see Stonerock, 2017[38]). Nevertheless, bygone studies have shown a clear therapeutic effect of pelvic floor exercises on erectile performance. In a study by Dorey et al, 40% of the treated patients achieved normal erectile function and in a further 34.5% a significant improvement in erection was observed. Only 25.5% of patients showed no improvement in erectile function.[41] In a very early study, Claes et al were able to show that in 150 patients with erectile dysfunction due to a venous occlusion problem after a physiotherapeutic intervention, 42% of the patients were so satisfied with the result that they rejected a planned operative measure.[44] In a major systematic review, Myers and Smith tried to clarify whether pelvic floor exercises are effective in the treatment of erectile dysfunction and to identify an optimal physiotherapeutic protocol for the treatment of erectile dysfunction (and premature ejaculation).[47] A total of 254 studies were screened, 24 studies were examined in detail, and 10 studies were used for the evaluation. 5 of these studies focused on the treatment of erectile dysfunction.[41,44,48–50] These 5 included studies used different physiotherapeutic protocols in terms of the frequency of supervised intervention (between 5 and 20) and the period of observation (3–4 months). Common to all studies was a daily training program carried out independently.[47] 2 studies included only pelvic floor exercises, 1 study combined pelvic floor exercises and biofeedback, and the remaining 2 studies combined pelvic floor exercises with biofeedback and electrostimulation.[41,44,48–50] In summary, the healing rate ranged from 35% to 47%.[44,49,50] As a limitation of these results, it must be mentioned that only in 1 study the IIEF-ED score was used as a control instrument for the therapeutic statement.[41] The other studies assessed the therapeutic outcome only by simple patient interviews (complete response, partial response, no response). The methodologically best study by Dorey showed a very good response (see above), as well as a significant improvement in the IIEF-ED score of 6.74 points after 3 months. Myers and Smith concluded that pelvic floor exercises (especially with the additional use of biofeedback, but probably also electrostimulation)

are an effective therapeutic option in the treatment of erectile dysfunction.[47] No recommendation could be made regarding the optimal therapy protocol, as the protocols used in the few studies were too different. Current recommendations suggest 2−3 therapy sessions per week and a combination of maximum (short-term) and sub-maximum (long-term) contraction exercises.[51,52] This combination of different compression intervals and strengths improves both the permanent increase in muscle tone (which supports erection) and the short-term strong muscle compression (which improves ejaculation control).[43,53] Cohen et al reported that with good strength and control of the pelvic floor muscles, many men with erectile dysfunction can produce a transient increase in rigidity of their erection through voluntary contraction of the pelvic floor.[43] On the other hand, increased muscle tone and overactivity of the pelvic floor muscles (as suspected in pelvic pain syndrome, eg) entail the risk of extrinsic compression of the internal pudendal artery, as well as possible impairment of the venous occlusion mechanism of the corpora, and thus erectile dysfunction.[54] In this respect, a functional training of the pelvic floor includes promoting proper contractions as well as proper relaxation. This is achieved by encouraging proper patterns and timing of the pelvic floor in its role in sexual function, as well as urinary and bowel function, and body's orthopedic movement system.[43]

We believe that diagnosing and treating pelvic floor dysfunction, and optimizing pelvic floor health, which may include ongoing performance of specific pelvic floor exercises, should be a permanent feature of the treatment for erectile dysfunction of different genesis (iatrogenic, venous leakage). We feel that intensive support and care of the patients is particularly important in view of the medium to long-term effect of this simple intervention, which is free of side effects.

Testosterone

Testosterone was isolated in the 1930s and defined as an important male sex hormone.[55] Different formations of testosterone have been used clinically since the end of the 1930s.[55] Despite its familiarity and clinical use, there have been controversial and extensive scientific and medical discussions about the physiological effects and clinical effects of this sex hormone. This ongoing, controversial discussion has prompted the Basic Science Committee of the Sexual Medicine Society of North America in 2016 to undertake a comprehensive review of the scientific, evidence-based data on the role of testosterone in sexual function and dysfunction.[56] The conclusion of this review (written by John Mulhall) paints a very sobering picture with regard to the basic scientific results available at that time: "There is no doubt that the approach to diagnosing and treating men with testosterone deficiency in the early 21st century is extremely crude-…Indeed, in practice, much of what we do falls under the banner of trial and error."[56] This judgment of Mulhall was a consequence of the fact that many scientific results concerning testosterone were generated from in vitro studies, found in animal models, and/or demonstrated on other tissues and in many cases only indirect conclusions could be drawn about the physiological and pathological situation in humans. Mulhall concluded by saying that he was very confident that he will be able to present better data on basic testosterone research in 2025.[56] In light of this sobering statement, the following comments on the influence of testosterone on the physiology and pathology of erection and the erectile mechanism of the penis should be used with caution.

With regard to the influence of testosterone on the erectile function of the penis, scientific studies essentially focus on the support of the tissue architecture of the erectile tissue, regulation of the tone of the smooth muscles as well as the influence on NO and cGMP regulation. Many research groups were able to show that androgen deprivation leads to typical changes in the erectile tissue. In endothelial cells, the androgen deprivation provokes an irregular surface and an impairment of cell-cell contacts, which leads to permeability and adhesion of erythrocytes on the endothelial cell surface.[57] Under the administration of testosterone these morphological changes are largely regressive.[57] In addition, a reduction of smooth muscle cells, and an increase in extracellular matrix and adipocytes in the cavernous body tissue were observed.[58,59] All these processes are considered to be degenerative and function-limiting. The tone of the muscle cells in penile vessels and the trabeculae of the sinusoids are largely responsible for the flaccidity and erection of the penis. As already explained (see above), erection is based on a complex molecular and fine anatomical interaction. Scientific studies have shown that testosterone has a supportive effect at various points in this complex interaction. For example, testosterone appears to stimulate and support the enzyme activity of nitrogen synthase (NOS), which is probably one of the most important molecular effects of testosterone in supporting the erection mechanism.[60] Furthermore, testosterone regulates the gene expression of many molecules related to the erectile mechanism (eg, nNOS, phosphodiesterase 5, alpha1-adrenoreceptor etc).[56] Additionally, there appears to be some direct effect of testosterone on muscle tone in erectile tissue. For example, the testosterone concentration present in the cavernous body (normal or at castration level) directly influences the response of the muscle cells to norepinephrine (contraction) in such a way that under locally lower testosterone concentration the muscle cells react much faster to norepinephrine with a contraction (and thus flaccidity of the penis).[61] In this respect, there are numerous indications of a direct and indirect influence of testosterone on erection. However, the objection formulated by Mulhall, which is easily understandable from the literature, still exists that the scientific findings were not made on human erectile tissue. For our clinical examination, however, the basic results are only of secondary importance. For the clinical application of testosterone in the context of the treatment of erectile dysfunction, high-quality clinical studies (set up in the light of basic scientific findings) are necessary. The European Male Aging Study was able to clearly

show on more than 3,400 men that erectile dysfunction is the most sensitive and specific indicator of a testosterone deficiency.[62] In this respect, a clinical influence of the testosterone deficiency on erection can be assumed. Unfortunately, the quality of the investigations in this field is also mostly not optimal, so that inconsistent results are available. A major disadvantage of many investigations is the use of different measuring instruments with regard to the therapeutic outcome. Often simple patient statements are defined as the final result of a study. This is all the more incomprehensible as the IIEF has been available for many years as a validated and reproducible instrument for measuring the results of erectile dysfunction treatments.[63] Most meta-analyses show a positive effect of testosterone therapy on erectile function.[64–66] However, other major review studies do not confirm these findings.[67,68] Corona and colleagues responded by including in the most recent meta-analysis only randomized and controlled studies (137 studies examined and 14 included) that used the IIEF score as an endpoint measurement tool.[69] Here, it could be shown once again, on a total of 2,298 patients included, that testosterone therapy (among other effects) is also an effective therapeutic agent for erectile dysfunction in men with testosterone deficiency. Depending on the severity of the testosterone deficiency (<12 nmol/L or <8 nmol/L), significant improvements in the IIEF score (1.47 and 2.95, a total of 2.31 points) were shown compared to the placebo group. However, according to the investigators, the observed overall effect of 2.31 points improvement in IIEF-ED under testosterone therapy only represents a clinically relevant improvement in patients with mild erectile dysfunction.[69,70] In summary, it can therefore be stated that especially in patients with a pronounced testosterone deficiency (<8 nmol/L) and a mild erectile dysfunction, a primary attempt can be made to treat both disorders with testosterone replacement therapy. It should be noted with limitations that metabolic conditions such as obesity and diabetes mellitus worsen the response.[69]

Of particular importance to us is the clear effect of testosterone replacement therapy as a strong supporter of physical activity, which (as described earlier) has a clearly positive effect on erectile performance.[40]

Of equal interest is the possible inducibility of the body's own testosterone production by vitamin D (see also below). A study by Pilz and colleagues showed that 165 patients who received 83 μg (3,332 IU) of vitamin D daily had a significantly higher testosterone level after 1 year than at the beginning of the study. The placebo group showed no change in testosterone levels.[71] Other studies could not show a correlation between vitamin D supplementation and testosterone serum concentration.[72,73] However, the application periods of 12–16 weeks were significantly shorter.

We believe that external supply of testosterone may be a primary treatment option in cases where mild erectile dysfunction coincides with testosterone deficiency. In cases of severe erectile dysfunction and testosterone deficiency, combination therapy (eg, testosterone plus lifestyle modification, and/or additional medication) should be used. The delayed time frame until the benefit of testosterone replacement therapy must be pointed out.

Nutraceuticals

The market for nutraceuticals for the treatment of erectile dysfunction is gigantic, confusing, and little regulated. In medical literature, the lay press, and the Internet, there are numerous scientific reports and marketing information on active ingredients and especially combinations of active ingredients that are supposed to have an effect on the erectile performance of the male penis. At first glance, sales promoting marketing information and scientifically based study results can hardly be differentiated. It is particularly difficult to gain an overview of the effect of the individual active ingredients because most offers contain combinations of active ingredients. Cui and colleagues have investigated the ingredients of the 30 best selling products for improving male sexual health.[74] They found up to 33 ingredients in 1 product. In this comprehensive review, the authors have tried to identify scientifically based information on the 20 most frequently used active ingredients (such as ginseng, zinc, vitamin B, L-arginine, Maca, dehydroepiandrosterone etc) of these combination products. The sobering conclusion of this work was that the scientific data on the effectiveness of the individual substances investigated were generally of low quality at that time.[74] In our investigations, we focus on only a few individual active substances for which randomized and controlled studies are available and whose presumed mechanism of action is consistent with the pathophysiology of erectile dysfunction. Certainly, further naturalzeuticals with erection promoting effects can be found in the medical literature, but detailed analysis of further substances would go beyond the scope of this overview. However, we would encourage searching the medical literature for substances that have a positive effect on the pathophysiology of erectile dysfunction and suggest appropriate treatment concepts or conduct corresponding studies.

L-Arginine/L-Citrulline

Without doubt, NO is one of the most important players in initiating and maintaining an erection (see above). It is therefore all too understandable that many producers of erection enhancing dietary supplements focus on the “raw material” for NO production in the human body, L-arginine. L-arginine is a semi-essential amino acid that occurs in relatively high concentrations in our food and is additionally synthesized from L-citrulline (another amino acid) in the human body.[75] During this process, amino acids contained in food (eg, glutamine and proline) are converted into L-citrulline in the enterocytes of the intestinal mucosa. In contrast to L-arginine, L-citrulline is not subject to hepatic elimination and is thus absorbed more efficiently from the systemic bloodstream. The absorbed L-citrulline is then converted into L-arginine in the kidney by the arginine succinate synthase and arginine succinate lyase (intestine-kidney

axis).[76] When nitrogen monoxide is synthesized from arginine by the addition of oxygen with the aid of NOS, L-citrulline is again formed as a by-product.[76] As a rule, there is no L-arginine deficiency, even in men with erectile dysfunction.[77] Nevertheless, Barassi and colleagues were able to show that, especially in patients with arterial erectile dysfunction, the serum levels for L-arginine and L-citrulline were significantly lower than in a control group, or in patients with non-arterial erectile dysfunction.[78] An older study showed that high-dose supplementation of 5 g of L-arginine daily for 2 weeks led to a significant improvement in erectile function (31%) compared to placebo (12%).[79] In the following years, a few high-quality studies were conducted which investigated arginine as a mono-therapeutic agent in patients with erectile dysfunction. Rhim and colleagues summarized these studies in a systematic review and meta-analytic study.[80] 540 patients with mild and moderate erectile dysfunction included in the meta-analysis demonstrate a significant improvement in erectile performance compared to placebo or no treatment. In the treatment and placebo groups, 8.3% and 2.3% of the patients demonstrated side effects, all of which were mild. The authors concluded that patients with mild and moderate erectile dysfunction would benefit from arginine supplementation. As a limitation of the study, scientists identified the very different dosages (1,500−5,000 mg/day), as well as the very different durations of application, which were probably the reason for the heterogeneity of the study results.[80] Additional information about the isolated effect of arginine can be obtained from combination studies in which a single agent control was undertaken. An example of this is the study by Gallo et al.[3] Also, in this study, treatment with arginine (2,500 mg per day) for 12 weeks alone showed a significant response in terms of IIEF-ED in mild (+5.4 points) and moderate (+2.5 points) erectile dysfunction. As expected, there was no significant effect in severe erectile dysfunction (+0.1 points).

A literature search for arginine, erectile dysfunction, and randomized controlled trials (RCT), based on the last 10 years, revealed a total of only 4 studies. Interestingly, 2 of these studies investigated the combination of L-arginine and Pycnogenol (a plant extract from the bark of the French Mediterranean pine).[81,82] In the older study, Ledda and colleagues examined 124 patients with mild to moderate erectile dysfunction. The treatment results were verified using IIEF-ED (questions 1−5 and 15). After 3 months there was a significant improvement in the IIEF-ED score from 15.2 ± 6.6 (baseline) to 25.2 ± 2.1, which improved further to 27.1 ± 2.1 after 6 months of therapy. In the placebo group, there was no significant change from the initial 15.1 ± 7.0 value compared to the 3-month 19.1 ± 3.0 and 6-month 19.1 ± 3.1 values.[81] In the more recent study, the authors treated 50 patients with moderate erectile dysfunction with the same combination of active ingredients and were able to achieve normal erectile performance (based on IIEF-ED results) within 4 weeks.[82]

Altogether it can be concluded on the basis of the available medical literature that the supplementation of L-arginine has a definite effect in mild and moderate erectile dysfunction. No conclusions can be made about the recommended daily dose and the application period due to the heterogeneity of the applied protocols. In severe erectile dysfunction, arginine has no place as a mono-therapeutic agent, but in combination with, for example, tadalafil it shows an additional effect which is statistically relevant (increased IIEF-ED from +4.9 to +6.6 points).[3]

Ginseng (Panax Ginseng)

Ginseng is a plant that is mainly found in Korea, China, and Siberia. The roots of the plants are marketed in 3 different forms for the production of medical-pharmaceutical products: fresh ginseng (<4 years old), white ginseng (4−6 years old, peeled, and dried), and red ginseng (>6 years old, steamed, and dried).[83] The active ingredients in ginseng are ginsenosides and ginseng saponins, which act by stimulating nitrogen synthetase (NOS), thereby increasing the supply of NO.[84] Ginseng is the most frequently used ingredient in the group of the 30 most frequently sold combination preparations for the treatment of erectile dysfunction mentioned earlier.[83] The dose used in combination products ranges from 10 to 150 mg. In this review, we will focus on the sole effect of ginseng in the treatment of erectile dysfunction. In the medical literature, we were able to identify 3 major systematic reviews that dealt at least partially with the effect of ginseng as a monotherapy for erectile dysfunction.[85−87] If one examines the included RCT in the reviews, it is quickly noticeable that all 3 papers refer to the same studies with only minimal exceptions. All studies included in the reviews were conducted between 1995 and 2013. From the 3 reviews we identified a total of 10 independent studies with a total of 614 treated patients. Unfortunately, 5 of the original papers were written in Korean, so we had to rely on the data summarized in the reviews or the abstracts. The studies were very heterogeneous with regard to the etiology or the extent of erectile dysfunction (psychogenic, vasculogenic, any kind, mild, and mild to moderate), the duration of treatment (4−12 weeks), the daily dose (1,400−3,000 mg, distributed over 2−3 single doses), the formation of ginseng (extract of ginseng berry, tissue-cultured mountain ginseng extract [CA Meyer], red ginseng), and the control instruments used (IIEF, global efficacy question, structured interview, Watts Sexual Function Questionnaire, and self-report). Overall, all studies found a good erection improving effect of ginseng therapy and reported only mild side effects in the form of stomach problems, headaches, and sleep disorders. In our opinion, the most meaningful meta-analysis was the one conducted by Borrelli and colleagues based on the IIEF results of 3 studies.[88−90] Patients in the 3 included studies were treated exclusively with red ginseng (n = 140) or placebo (n = 96). A meta-analysis of IIEF baseline values to IIEF values after 8−12 weeks of treatment showed a standardized mean difference

of 0.43 (95% CI 0.15−0.70) for the treatment group.[87] Overall, based on the available medical literature, we conclude that ginseng might improve erectile performance in mild and moderate erectile dysfunction. Somewhat questionable are the relatively low amounts of active ingredients used in combination preparations (10−150 mg) compared to the mono-preparations (1,400−3,000 mg).

Vitamin D

Vitamin D is a fat-soluble vitamin that is found in large quantities in foods such as fish, milk, avocado, and mushrooms and is a steroid hormone in terms of its chemical structure (and is therefore often called vitamin D hormone). More than 40 metabolites of vitamin D exist in human serum, but only the end product 1,25-dihydroxyvitamin D performs its biological function.[91] The function of vitamin D and calcium in the mineralization of bones is well-known and scientifically studied.[92] In addition to the effect on bone mineralization, vitamin D influences numerous other bodily functions, such as the immune system and the cardiovascular system.[93] Especially in recent years, there has been increasing evidence of the association of vitamin D with endothelial cell function and cardiovascular health.[94] For example, a study involving more than 7,000 patients showed a clear association between low vitamin D serum levels and cardiovascular diseases such as hypertension, coronary heart disease, and the corresponding risk factors such as diabetes mellitus and hyperlipidemia.[95] Vitamin D mediates its action via a membrane-bound receptor (vitamin D receptor), which is found in almost every tissue type in the human body.[91] More than 3,000 genes are influenced by vitamin D, whereby vitamin D mediates its biological effects via genomic and non-genomic downstream effects.[96] A vascular effect of vitamin D is the induction of NO production by eNOS in endothelial cells, which mediates vascular dilatation.[97] Since, as already shown, there is a close correlation between endothelial cell function, cardiovascular health, and erectile function, it is important to look for direct connections and the connection of erectile dysfunction and vitamin D. This correlation is all the more probable because the activation of NO also plays an important role in vasodilation during erection. In addition to the direct, vasodilating effect of vitamin D via NO, the influence on testosterone serum concentration (see above) is a further indication of the effect of vitamin D on erection. In addition to testosterone stimulation, vitamin D is probably also capable of directly mediating testosterone activity by binding to the testosterone receptor.[98] A recent meta-analysis, based on 7 studies and data from 4,132 patients, concerning vitamin D serum concentration and erectile dysfunction showed a mixed picture, wherein erectile dysfunction is not automatically associated with low vitamin D concentration.[99] However, this meta-analysis initially found a very clear connection between low vitamin D serum concentration and the presence of erectile dysfunction. But when the authors excluded the largest study with more than 3,000 patients (which showed a clear correlation and can therefore falsify the overall result in comparison to smaller studies with negative results) from the analysis in a subgroup analysis, the positive result could not be confirmed.[99,100] Since the genesis of erectile dysfunction is multifactorial and individual factors can be more or less pronounced in individual cases, a mixed picture can be drawn when evaluating a single factor. For example, Barassi and colleagues were able to show that patients with arterial erectile dysfunction in particular had low vitamin D value and this correlated with the severity of erectile dysfunction.[101] In this study, patients with mild erectile dysfunction (IIEF-5, 16−20 points) showed a vitamin D value of 26.1 ng/mL and patients with pronounced erectile dysfunction (IIEF-5, <10) a vitamin D value of 19.8 ng/mL.

Based on the available medical literature, we believe that supplementation of vitamin D is probably useful for improving erectile performance due to several activities of this steroid hormone: (i) the direct effect on NO synthase and associated NO increase, (ii) the possible stimulating effect on testosterone production, and (iii) the direct stimulation of the testosterone receptor.

Supplementation of vitamin D is not a trivial matter. Until 1998, vitamin D deficiency was found to occur when the serum concentration of 25-hydroxyvitamin D (which represents the total concentration of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3) was below 10 ng/mL and was equated with the occurrence of rickets.[102] In 1998, vitamin D deficiency was defined as a bone health-related deficiency at 25-hydroxyvitamin D3 (25(OH)D) serum concentrations of <20 ng/mL.[103] Later studies conclude that the maximum musculoskeletal health requires serum levels of at least 30 ng/mL.[104] In addition, a normal value of 20 ng/mL means that about 36% of the population in the United States and about 92% of the population in Northern Europe have a vitamin D deficiency.[105] This high incidence of vitamin D deficiency in the population is despite the fact that in many countries (eg, United States) important staple foods (eg, milk) are supplemented with vitamin D.[105] Worldwide, it is assumed that about 1 billion people suffer from vitamin D deficiency.[105] One of the main causes of this vitamin D deficiency pandemic is essentially due to the production of this important vitamin by ultraviolet B (UV-B) irradiation of the human skin. Since UV-B irradiation leads to sunburn in the short term and the development of melanoma in the longer term, the necessity of UV-B irradiation for vitamin D production contradicts our skin cancer prevention strategies.[105] In this respect, supplementation of vitamin D beyond the influence on sexual health is sensible and probably necessary in many cases anyway.

2 different forms of vitamin D are available for supplementation, namely vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). According to recent studies, both forms are suitable for vitamin D supplementation. It is important to note that vitamin D3 is of animal origin, so vegans should be prescribed vitamin D2 (which is obtained from yeast).[105] According

to our research, there is no recommended level of vitamin D serum that is associated with a particularly positive effect on erectile performance; so you should follow the general recommendations for supplementing vitamin D. To achieve an average serum concentration of 40−60 ng/mL of 25-hydroxyvitamin D, a daily supply of 4,000−5,000 IU of vitamin D2 or vitamin D3 is required.[106] Particularly obese men (body mass index >30) need 2−3 times this dose to achieve a corresponding effect.[107] The Institute of Medicine (USA) reported in its 2011 report on supplementation with calcium and vitamin D a continuous decrease in general mortality up to a serum 25-hydroxyvitamin D value of 30 ng/mL and described a slight increase in general mortality from a serum value of 50 ng/mL.[108] This observation became the subject of several studies that tried to reveal the reason behind the increased mortality. As a serum level of 50 ng/mL can hardly be achieved naturally, it can be assumed that all these patients were given vitamin D. Holick et al concluded that the increased mortality of the female patients (in men the increased mortality could not be detected) was probably due to the pre-existing vitamin D deficiency.[107]

Since vitamin D is a fat-soluble vitamin that can accumulate in the body, medical literature also shows critical comments on high-dose supplementation.[105] However, despite the fat solubility of vitamin D, intoxication is extremely rare and only possible if excessive doses are taken over long periods of time.[105] Due to the extensive studies, high safety profile, and the positive effects on erectile function, we support the idea to include vitamin D in the therapeutic armamentarium of erectile dysfunction. Especially in patients with mild erectile dysfunction and testosterone deficiency, an attempt can be made to increase testosterone with vitamin D.

Curcumin

Curcumin (diferuloylmethane) is the predominant curcuminoid from the rhizome (rootstock) of the turmeric plant (*Curcuma longa*) and is an ingredient of the spice named curcuma.[109] Curcumin is believed to have therapeutic effects in diseases as diverse as cancer, diabetes, and cardiovascular disease.[110,111] It has anti-inflammatory and antioxidative effects by influencing different regulatory circuits.[112] In the medical literature, there are only few studies on the use of curcumin in men with erectile dysfunction. The reason why we have included this active ingredient here is the numerous animal experimental results regarding support of the erectile mechanism and the known strong effect on the endothelial function of the blood vessels.[113] Studies in rats (which suffered from diabetically induced erectile dysfunction) have shown that curcumin significantly increases the concentration of NOS, cGMP, and HO-1 in the erectile tissue. This increase in NOS, cGMP, and HO-1 was accompanied by increased pressure in the cavernous bodies after electrostimulation of the cavernous nerve of these rats.[114] In the meta-analysis of Hallajzadeh et al, a significant effect of 4−24 week curcumin administration of 45−2,000 mg/day on the flow-mediated vascular dilatation was observed.[113] Different formations of curcumin were used (curcumin, curcuminoid, rhizome of *C. longa*). The differences with regard to the formation and dosage used, as well as the clearly different application periods, ultimately do not allow an assessment of the appropriate form of therapy for a man with erectile dysfunction. Some studies point to the poor water solubility of curcumin and the associated poor bioavailability.[114,115] To circumvent this problem, water-soluble curcumin derivatives were produced and tested against conventional curcumin in animal experiments. Here, especially in the Zaahkouk et al study, a clear effect of the conventional curcumin was shown, which lasted up to 1 week; so we assume that the natural substance is sufficiently bioavailable and effective.[114,115] Of particular interest to us is the well-documented effect of curcumin on the healing of spinal cord injuries.[116] In a meta-analysis 8 animal studies were summarized. In total, statistically significant effects regarding biochemical parameters (antioxidative effect) and better functional outcome of the curcumin-treated animals were reported. With regard to the dosage used, the range was 30−300 mg/kg curcumin and application duration was once post trauma to 1 day before trauma and 7 days after trauma. In this respect, there was again a wide range of different forms of therapy for this treatment. 2 studies using 40 and 100 mg/kg for 7 days after trauma showed particularly good functional results.[117,118]

Based on our literature research, we conclude that curcumin cannot be recommended as a general medication for men with erectile dysfunction due to insufficient data. However, we see an application in connection with neurologically induced erectile dysfunction, for example in the context of a radical prostatectomy. On the basis of the data from the meta-analysis, albeit purely animal based, which also showed a dose-dependent effect, one should probably aim for relatively high doses (1,000 plus mg/day) around the surgical procedure.[116] Whether this has a positive effect on the severity of erectile dysfunction after radical prostatectomy needs to be clarified in prospective studies.

PSYCHOTHERAPY/COUNSELING

As described earlier, erection is based on a coordinated interaction of vascular and neural structures, as well as hormonal, molecular, and psychological factors. It has long been known that neurological-psychiatric diseases (Parkinson's, multiple sclerosis, Alzheimer's, depression, and schizophrenia) are often associated with erectile dysfunction and other sexual dysfunctions.[119] Since an increased sympathetic tone counteracts the development and maintenance of an erection, mental health plays a particularly important role. In this respect, it is only too easy to understand that, in addition to erectile dysfunction triggered by purely neurological-psychological factors, each longer existing erectile dysfunction has a psychological component.[119] With the introduction of PDE5I in the late 1990s, the psychological component of erectile dysfunction was largely neglected in favor of drug therapy. Only when it became apparent that a high percentage of patients discontinued drug therapy, despite its good effect and

safety, was the importance of psychological integrity for the erectile process rediscovered.[120] Myths circulating in society regarding sexuality and cognitive distractions are sufficient to compromise an erection process, that otherwise functions in all components, in such a way that the development and maintenance of an erection become difficult or impossible. Socially anchored myths, such as "It is the man's responsibility to satisfy the woman" or "A man can and wants sex at any time," were already collected in the 1980s.[121] Cognitive distractions such as "I'm a complete failure because my erection was not 100%" or "I'm sure it won't work tonight" have also long been known as erection killers (even despite drug support for the erection).[122] In this respect, possible psychological impairments (primary or secondary) should already be considered during the sexual history and attention should be paid to this problem in the therapeutic discussion. It is essential that the psychological consideration includes the impairment of the couple's relationship, which is often caused by erectile dysfunction.

Although men may wish to discuss sexual problems with their doctor, most men find it extremely difficult to initiate such a conversation.[123] Depending on the situation, which is unfamiliar and unpleasant for the patient, an uncomplicated and supportive atmosphere of communication must be created so that the psychological component of erectile dysfunction can be understood, and appropriate treatment can be initiated.

Psychological-psychiatric treatment can be the core therapeutic approach for erectile dysfunction primarily caused by psychological factors. Here, the treatment of the causative underlying psychological disease, such as depression or schizophrenia, is the therapeutic focus. However, as already mentioned earlier, even organically based erectile dysfunction usually carries a psychological component, the perception and therapy of which can be essential for the overall success.

Psychological instruments such as the "Sexual Tipping Point" concept can, in addition to the diagnostic aspect, also achieve a therapeutic effect that should not be underestimated due to visualization of the various influencing factors.[124,125]

Patients with impaired erectile function (regardless of its etiology) who do not respond adequately to different therapeutic concepts can be helped to restore a fulfilling and satisfactory sex life by applying psychological concepts such as the "Good-Enough Sex Model."[126] This psychological instrument shifts the attention of sexuality, in 12 essential principles, from the sexual performance to sexual pleasure.

In summary, in our opinion, the treatment of erectile dysfunction should always be combined with causal and therapeutic knowledge transfer, as well as psychological support and counseling for the patient/couple adapted to the situation.

VACUUM PUMP REHABILITATION

Vacuum erection pumps were developed by Geddings D. Osbon in the 1960s and were approved by the U.S. Food and Drug Administration in 1982 for marketing as a non-invasive treatment method for erectile dysfunction.[127] In the 1980s and 1990s more than 150,000 erection pumps were prescribed to patients annually in the United States alone. With the introduction of PDE5I, the number of prescriptions fell significantly in favor of drug therapy. For the symptomatic treatment of erectile dysfunction, there is now only a small group of patients (especially couples in long-term relationships) who primarily use the erection pump.

In the last 5−10 years in particular, the erection pump has experienced a renaissance, but not as a primarily symptomatic treatment method, but rather as a rehabilitation instrument for long-term restoration or improvement of erection after, for example, a radical prostatectomy.[128,129] The path mechanism of long-term erectile dysfunction, for example in the context of prostatectomy, is based on an initial erectile dysfunction caused by neuropraxia during surgery.[128] This erectile dysfunction, which is probably only temporary (up to 3 years), then leads to tissue hypoxia and irreversible erectile tissue fibrosis due to the absence of erection at night and sexually stimulated erection.[130] Bosshardt et al were able to show that a large amount of oxygenated blood (58% arterial and 42% venous blood) can be directed into the erectile tissue with the aid of the vacuum pump.[131] Numerous studies have shown that regular erections produced by a vacuum pump with a significant increase in the partial pressure of oxygen in the blood of the erectile tissue prevent pathophysiological processes of the formation of erectile fibrosis.[132−134] The mechanism that leads to erectile dysfunction in the context of erectile tissue fibrosis is the defective venous occlusion mechanism.[128] It has been shown that an early start of vacuum pump therapy (1 month after surgery vs 6 months after surgery) leads to better treatment results.[135] The extent to which vacuum pump therapy can achieve a reversal of the already developed erectile tissue fibrosis or an already manifest venous leakage is not scientifically answered.

Yang and colleagues identified optimal negative pressures for vacuum pump therapy at −200 mmHg. Lower pressures did not produce a better effect in their study.[133] In the course of symptomatic treatment with vacuum pumps and application of a constriction ring, it was shown that after 30 minutes ischemia occurs due to the exhaustion of oxygen present in the blood.[131] The therapy has a few side effects (occasional bluish skin discoloration) and few contraindications, such as recurrent priapism, or clinical pictures that promote priapism, such as sickle cell anemia and leukemia. Caution ist advised when taking anticoagulants (celty Acetylsalicylic acid, Marcumar etc). Within the framework of causal therapeutic concepts, we believe that the constriction ring should be avoided, and erection should occur more frequently via the vacuum mechanism (eg, 3 times for 3−5 minutes each time).

We recommend the integration of erection pumps in rehabilitative and/or causal therapeutic concepts, especially for patients who only rarely have sexual intercourse and who do not

succeed in achieving an erection sufficiently frequently. In the purely symptomatic treatment of erectile dysfunction, the vacuum pump is also successfully used in otherwise therapy-refractory cases, such as after removal of a defective penile prosthesis.[127]

SHOCK WAVE THERAPY

In 2010, an Israeli research group published a first paper on the effect of low-dose extracorporeal shock wave therapy (ESWT) in patients with erectile dysfunction.[136] Within this study, 20 patients with vascular erectile dysfunction undertook two 3-week treatment cycles each, 2 treatments per week with a 3-week pause interval. This pilot study already showed a very good effect of the treatment after only 1 month. The IIEF-ED score improved within this time from 13.5 + 4.1 to 20.9 + 5.8. After 6 months the picture was unchanged. It was particularly noticeable that after 6 months half of the patients (n = 10) no longer needed PDE5I to achieve an erection capable of sexual intercourse.[136] This observation in particular, and the hope associated with it that this method would provide a causal therapy for erectile dysfunction, led to a large number of scientific studies on ESWT and erectile dysfunction in the following years. Various studies investigated the best indication, the most effective intensity of the shock waves, the best number of treatments, the long-term effects of the treatment, as well as the underlying mechanisms of action of shock waves on the erectile tissue. In a large review and meta-analysis, Lu and colleagues summarized the results and progress achieved in previous years.[137] The authors concluded that ESWT has a definite effect on erectile dysfunction of different etiologies. The review was based on the results of a total of 14 studies and 833 patients included. However, only 7 RCT were found for the meta-analysis. The remaining studies were simple cohort studies. Only 5 of the 7 randomized trials could be used to assess treatment success using the IIEF-ED questionnaire. 3 of the 5 studies showed a significant improvement in the IIEF-ED score after treatment.[138–140] However, it is striking that in a study by Zimmermann and colleagues, patients with pelvic pain syndrome were treated and erection improvement was only an additional observation. Here, a direct effect of ESWT applied to the perineum and not to the erectile tissue should not really be expected. Rather, it can be assumed that patients who experienced a significant improvement in pelvic pain syndrome also experienced an improvement in erection as a result.[140] Poulakis et al found no improvement in the IIEF-5 score, although in this study only patients with Peyronie's disease were treated.[130] Of the 53 patients treated with ESWT, 91% (48 patients) complained of painful erection before treatment. The patients received only 3–5 treatments in total at intervals of 1 week, 0.07–0.17 mJ/mm^2 energy density, and 2,000 pulses per treatment. Whether the erectile tissue was treated in several places or only focused on the plaque remains unmentioned. 74% of patients (n = 39) in the ESWT group reported a significant reduction in pain after treatment ($P < .001$). As in the control group also 57% of the patients (n = 8) reported a significant improvement of pain, no significant result was found in the comparison of the 2 groups. The ESWT treatment had a significant effect on penile angulation, which was reduced by 11° in the treatment group, which also reached the significance level compared to the control group ($P < .001$). Nevertheless, patients still showed a mean deviation of 35° after ESWT treatment (previously 44°), which may be responsible for the poor outcome in terms of IIEF-5 (mean IIEF-5 before treatment 11 [range 8–19] and after treatment 12 [range 8–18]).

The second study mentioned in the meta-analysis with negative outcome is the study of Yee and colleagues from 2014.[141] Here, 30 patients who had suffered from erectile dysfunction for more than 6 months were treated with ESWT (2 cycles of 3 weeks with 2 treatments per week, energy density of 0.09 mJ/mm^2, and 1,500 impulses, which were distributed at 5 different locations on the penis [300 impulses each]). 4 weeks after the end of the second treatment cycle, the patients were re-evaluated. At post-examination, no significant improvements in erectile function were found in IIEF-ED compared to the baseline or the control group. In a sub analysis, however, the authors were able to show a significant improvement in IIEF-ED in patients with pronounced erectile dysfunction despite the short control interval of 4 weeks (IIEF-ED improvement of 10.1 + 4.1 points vs control group 3.2 + 3.3 points, $P = .003$).[141]

The review and meta-analysis attempted to identify an optimal treatment protocol.[134] Parameters examined were the energy density of the shock wave, the number of pulses per treatment, the number of treatments per week, the number of treatment sites, and the number of treatment cycles in weeks. The best treatment protocol could not be identified due to the different parameters used and the small number of examinations. However, there was a tendency to show better effectiveness with a low energy density (0.09 mJ/mm^2), an increased number of pulses (3,000 per treatment), and shorter treatment intervals (<6 weeks). One major advantage of the treatment method is considered to be its repeatability and the few side effects. In our opinion, ESWT may have a definite value in the treatment of erectile dysfunction as a non-invasive method with few side effects. Due to the presumed mechanism of action via an increase in vascular cross-section, by the induction of angiogenesis, as well as stimulation of cell proliferation (smooth muscle cells and endothelial cells in the erectile tissue) and tissue regeneration, ESWT very well fits the concept of a curative and regenerative therapy of erectile dysfunction.[142,143] However, more independent, comparable, and long-term studies are needed to prove this effect. A disadvantage of the ESWT treatment is the repetitive character of the treatment (complex therapy, poor patient compliance), as well as the relatively high therapy costs.

CONCLUSIONS AND POSTULATES ON ERECTILE DYSFUNCTION

The collected data on the pathology and treatment of erectile dysfunction allow a differentiated consideration of this common male problem. Drug therapy with PDE5I represents a very good and rapidly effective, but symptomatic, treatment. However, in medium and long-term treatment, we see multidimensional and differentiated therapy options integrated into various treatment concepts.

Based on the data collected on the effectiveness of different therapeutic measures and medications, we could imagine integrated concepts for the treatment of different forms of erectile dysfunction; for example, the combination of L-arginine/L-citrulline and ginseng for the treatment of mild erectile dysfunction, or the combination of curcumin and vacuum pump rehabilitation as part of erectile rehabilitation after radical prostatectomy. Combinations of vitamin D and ginseng in the treatment of mild and moderate erectile dysfunction combined with libido deficiency and a lowered testosterone serum level would certainly be interesting. Psychological support, counseling, and lifestyle changes and psychotherapy/counseling should regularly be integrated into the treatment of erectile dysfunction. The integration of PDE5I (as an on-demand or continuous dose) into any erectile dysfunction treatment regimen can of course be helpful and valuable.

In order to get closer to a cause-related therapy of the different underlying causes of erectile dysfunction, further scientific studies are required. In order to advance scientific research in a meaningful way, we have come up with a number of postulates, the implementation of which we believe can improve the therapy of erectile dysfunction to a high medical level.

Based on our research and the resulting considerations, we offer the following postulates for the diagnosis and treatment of patients with erectile dysfunction:

1. We need to define different erection types—neuronal/vascular, central/peripheral, visual/tactile—and to understand their molecular physiology. The defined erection type must then be included in diagnostic and especially therapeutic considerations.
2. Multimodal therapy concepts should be conceived, investigated, and implemented based on the pathophysiology of erectile dysfunction and a detailed investigation of causation.
3. It is noticeable that large meta-analyses concerning the therapeutic effects of supplements always refer to older studies. In addition, the study quality is usually low, and the treatment protocols used are very heterogeneous with regard to formation, dosage, and control instruments; up to date, standardized studies are needed.
4. When investigating the effects of different therapeutic approaches, treatment periods of 4−12 weeks are usually examined. With long-term development of erectile dysfunction, such short-term therapy concepts seem unrealistic to us. Study periods of >12 months should be a minimum period for the evaluation of therapeutic components and procedures.
5. Realistic and honest coaching of patients is much needed in many presentations. This intensive care of patients cannot be provided by a treating urologist/andrologist and must be provided by digital products or well-trained assistants (men's health medical assistant).
6. Erectile dysfunction in the vast majority of affected men is typically treated with non-cause-specific treatment methods; this must change.

Perhaps through concerted scientific action we will enable future therapists to replace the mere symptom-therapeutic erection production—comparable to the clumsy flapping of Stanley Beamish's wings/arms—with a long-term causal-therapeutic intervention that comes close to natural erection—comparable to the skillful flight of a hawk and so, the circle is complete.

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