

A Comprehensive Review of Erectile Dysfunction in Men with Diabetes

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Abstract

▼
 Erectile dysfunction (ED) is more common in men with diabetes (DM). Dependent on the selected population, age, DM type and duration, the prevalence of diabetic ED (DED) varies from 32 to 90%. In 12–30% of men ED is the first sign of diabetes, diagnosed later. Today men with diabetes live longer than ever, and develop more late diabetic complications. Having in mind also the global ageing of the world population all this data suggests an increasing number of men with DED in the future. The main factors playing in the complex pathogenesis of DED are diabetic neuropathy (oxidative stress, polyol pathway, advanced glycation end-products, nerve growth factor deficiency, dysfunction of protein kinase C, tissue remodeling, etc.), macrovascular arterial disease (endothelial dysfunction, abnormal collagen deposition and smooth muscle degeneration, dyslipidemia, arterial hypertension, veno-occlusive dysfunction, etc.), hypogonadism, structural remodeling of the corporeal tissue, psychogenic components and adverse drug reactions. The diagnostic process is based on the results of questionnaires, neurological, vascular (Doppler) and other more rarely used investigations.

Introduction

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 According to the 6th edition of the International Diabetes Federation Diabetes atlas (2013) nowadays, there are 382 million people with diabetes mellitus (DM) in the world. The global prevalence is 8.3% of the adult population, and the disease causes at least 548 billion US\$ in health expenditure=11% of total health spending on adults. The prognosis is alarming – in 2035 it is expected the number of people with diabetes to be 592 million with a global prevalence of 10.1% (IDF, 2013). Over the past 2 decades DM has

Because of the complex pathogenesis of DED diabetic men represent a “difficult” treatment group. The difficulties are from the “beginning”, because patients do not talk about their problem spontaneously, and doctors do not ask about it. The treatment of DED should be team work, preferably including also specialists in sexual medicine. Psychological support and counseling of the couple is necessary in most cases. The *general measures* include implementation of a healthier lifestyle, improved glycemic-, lipids-, and arterial pressure control, and careful re-evaluation of the concomitant medications. The *specific treatment* includes as first line therapy the inhibitors of phosphodiesterase type 5 (PDE-5) with lesser effectiveness compared to non-DM men. There are rare studies with selected diabetic populations and even less with head-to-head comparisons between the PDE-5 inhibitors. Men with DM have a higher prevalence of hypogonadism. Testosterone replacement therapy should be started in symptomatic men with proven hypogonadism and no contraindications. Vacuum constriction devices and intracavernous or intraurethral applications of vasoactive drugs are the second line therapy. Vascular surgery rarely comes into consideration. The penile implant is the last and effective option in men with severe DED.

become an epidemic, mostly because of type 2 (DM2), which represents 90–95% of the cases with DM, although the incidence of type 1 (DM1) has also doubled (Ryan, 2009). The physical, emotional, financial and social burden of DM is caused mostly by late complications of diabetes (○ Fig. 1).

The progress in understanding the pathogenesis of DM, the increased perception and sensitivity of society, and the broad spectrum of therapeutic tools in the last years has led to the practical elimination of ketoacidosis and other acute diabetic complications as a cause of death in

developed countries, and to the improvement of glucemic control to the highest level so far. These favourable factors made it possible today for people with DM to live longer than ever, which increases the chance of developing late complications of the disease. Thus, demographic tendencies and epidemiological prognoses highlight an increasing importance of chronic diabetic complications in the future including diabetic erectile dysfunction.

Erectile dysfunction (ED) is the persistent or recurrent inability to attain or maintain an erection sufficient to complete sexual intercourse or another chosen sexual activity. During the last 15 years the scientific interest towards ED grew significantly because of:

1. Aging of the population and in particular the increasing life expectancy of men. The prevalence of ED increases with age. According to a WHO report (2008) it is expected that 35% of the population will be over 60 years in industrial countries in the year 2025 (NIC, 2008).

2. ED is common in men of all nations. As discussed below, the global aspects of the problem "Erectile dysfunction" were demonstrated in several large epidemiological studies.
3. There is increasing evidence of a direct link between ED and cardio-vascular diseases. ED is a marker of the vascular and in particular endothelial health of a man and it can be considered not only as a part of the quality of life but also as a predictor of its quantity (length) as well.
4. The release of the first PDE-5-inhibitor (sildenafil) on the market about 15 years ago, followed by vardenafil, tadalafil, avanafil and others, revolutionized the treatment of ED making it more effective, accessible, safe and cheap.

The prevalence of DM is increasing dramatically and it has been recognized as a pandemic disease. After the introduction of sildenafil in 1998 the number of publications about diabetic erectile dysfunction (DED) rose consistently (• Fig. 2). Although ED is present in many non-diabetic men, DED may be considered as a late diabetic complication because to the above mentioned reasons some diabetes-specific aspects should be added:

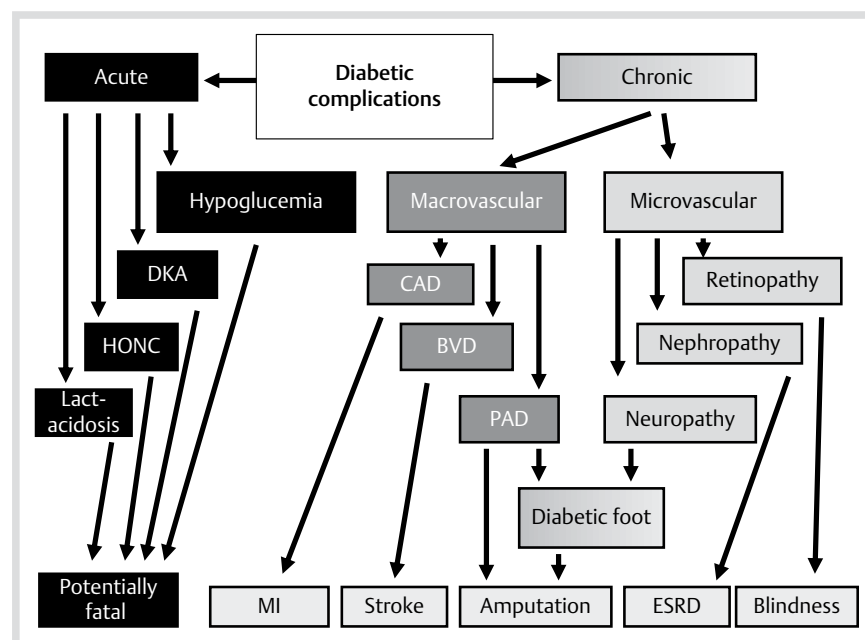


Fig. 1 Diabetic complications. DKA – diabetic ketoacidosis; HONC – hyperosmolar nonketotic coma; CAD – coronary artery disease; BVD – brain vascular disease; PAD – peripheral artery disease; MI – myocardial infarction; ESRD – end-stage renal disease.

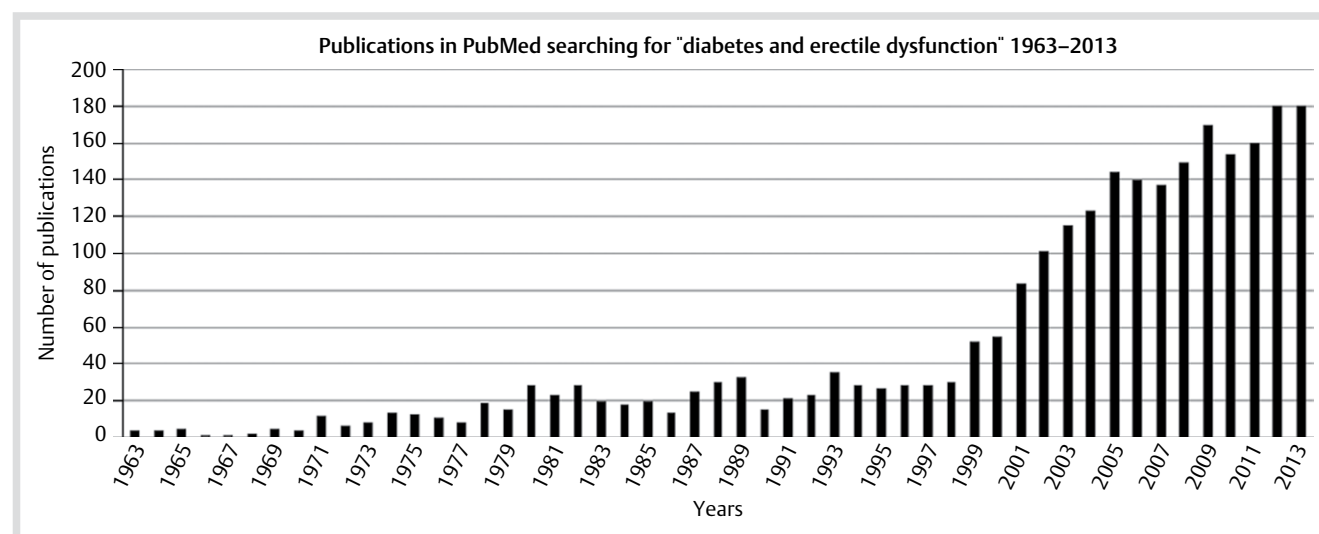


Fig. 2 Scientific publications during the last 50 years found in PubMed searching for "diabetes and erectile dysfunction".

5. The prevalence of ED in men with DM is higher compared to healthy men.
6. Pathogenesis of DED is specific and more complex compared to non-diabetic one.
7. ED is more severe and impacts more profoundly the quality of life of diabetic men.
8. The effectiveness of the treatment for DED is lower compared to men without DM.

Prevalence of DED

Depending on the age, duration and type of DM and the used diagnostic criteria epidemiological data about DED vary significantly between different studies. The evolution of DM2 commonly includes several pre-diagnostic stages, each including several years: insulin resistance and metabolic syndrome, pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance), and undiagnosed diabetes. Many patients already have ED at the diagnosis of the disease. By analogy with the prediction of coronary artery disease, ED has been proven to be the first sign of diabetes, diagnosed later in 12–30% of men (Lewis, 2001; Adegite et al., 2009). A recent study found in a sample of 499 men (mean age 58.8 ± 8.8 years) with new or recently diagnosed DM2: mild DED in 19.4%, mild-to-moderate in 15.4%, moderate in 10.4%, and severe in 21.6% of patients (Corona et al., 2014). ED is 3–4 times more common in diabetics compared to the general population (Martin-Morales et al., 2001; Feldman et al., 1994). During the first 10 years after the diagnosis of DM, DED is established in more than half of the men (Vinik, Richardson, 1998). We found a prevalence of DED of 44.7% among diabetic men aged 53.0 ± 12.5 years with diabetes (74% DM2) duration of 8.6 ± 6.7 years and mean BMI 29.0 ± 4.3 kg/m² (Kamenov et al., 2007). Reviewing the literature Malavige, Levy (2009) estimated a range of 35–90% reported in different studies from different countries (Malavige, Levy, 2009). The prevalence of ED in type 1 diabetes (DM1) is 32% and in type 2 (DM2) it is 46% (Vickers, Wright, 2004). According to 2 studies from different countries the prevalence of DED increases from 9% in the age interval 20–29 years and 15% between 30–34 to 95% in 60–70-year-old men and this increase correlates with the duration of diabetes, poor metabolic control and diabetic complications (Fedele et al., 1998; Smith, 1981). Multivariate analyses of several population based cohorts show that of all risk factors diabetes impacts the highest risk for ED with an age adjusted relative risk of 1.3–3 depending on diabetes type (Chitale et al., 2009a; Chitale, 2009b.; Bacon et al., 2002; Johannes et al., 2000).

Pathogenesis of DED

Detailed description of the physiology of erectile function (EF) is not an object of this paper. In short, the **erection** is a complex process in which psychological, social, endocrine, paracrine, neural, vascular and other factors take part. The penis is a hydraulic organ whose state – from relaxation to different phases of erection is determined by the grade of fullness with blood of corpora cavernosa. Their volume is defined by 2 variables – arterial inflow and venous outflow. The capacity of the filling terminal helical arteries is determined by NO-dependent smooth muscle relaxation. Different stimuli – psychogenic (vis-

ual, auditory, olfactory, memory, fantasy) or reflectory (tactile) activate the central and/or peripheral neuronal chains leading to synthesis and secretion of NO from the non-adrenergic–non-cholinergic (NANC) neuronal terminals in the cavernosal bodies through activation of neuronal nitric oxide synthase (nNOS). This small amount of NO triggers initial smooth muscle relaxation starting the hemodynamic process of erection. Further, receptor mechanisms and the shear stress in the vascular wall activate phosphatidylinositol-3-kinase/protein kinase B (Akt) pathway leading to activation of endothelial nitric oxide synthase (eNOS) and further NO release from the penile endothelial cells. Binding of the released neural and endothelial NO to soluble guanylate cyclase in the smooth muscle cells (SMC) increases cyclic guanosinemonophosphate (cGMP) levels and cGMP-dependent protein kinase G (PKG) activity. As a consequence cell membrane Ca-channels are closed decreasing the Ca⁺⁺ influx in the cell and from the other side cytosolic Ca⁺⁺ is retained in the endoplasmic reticulum. The opening of the Ca-dependent potassium channels on the membrane leads to potassium outflux and hyperpolarization. Finally, the cytosolic Ca⁺⁺ depletion causes cavernosal SMC relaxation leading to increased blood inflow through the helical arteries, sinusoidal filling and cavernosal dilation. The volume of corpora cavernosa increases and a compression of the draining venous vessels (emissary veins) in subtunical venular plexus against the rigid tunica albuginea occurs with a consequence – venous occlusion, decrease of outflow and further increase of intracavernosal pressure. The process of erection needs an intact cavernosal structure, characterized by abundant elastic fibers and less collagen.

The **detumescence** initiates with activation of the sympathetic neurons and liberation of norepinephrine from the adrenergic terminals of the cavernosal nerve, as well as endothelins and Pgf_{2α} from the endothelial cells covering the cavernosal sinusoids. An increase in intracellular calcium activates myosin light chain (MLC) kinase and phosphorylation of MLC to generate SMC contraction. Additional pathways such as RhoA/Rho-kinase lead to the sensitization of the SMC contractile apparatus to calcium, promoting contraction. Activation of Rho-kinase results in inhibition of MLC phosphatase and continued expression of phosphorylated MLC. The RhoA/Rho-kinase pathway is a predominant calcium-sensitizing pathway to mediate continuous smooth muscle tone in the penis. Protein kinase C (PKC) is also calcium sensitizing and acts to inhibit MLC phosphatase, also promoting the contractile response (Hidalgo-Tamola, Chitale, 2009).

Disturbances of each of the described consecutive stages from the erotic stimuli to the venous drainage may compromise the process causing ED. The pathogenetic concept about ED evolved from the mostly psychogenic in the past to the leading organic currently. It should be mentioned that psychogenic and organic disturbances interplay in every case of ED and cannot be separated absolutely even for didactic reasons. The similarities of dilatation mechanisms in corpora cavernosa and the remaining arterial vessels in the body, based on the key role of NO, explain the common mechanism of their deterioration in endothelial dysfunction. The presence of cardio-vascular disease increases significantly the likelihood for ED (Martin-Morales et al., 2001). From the other side, ED may be the first sign of existing but still undiagnosed CVD (Montorsi et al., 2003).

The pathogenesis of DED is much more complex compared to non-diabetic men (● Fig. 3). During the last years special atten-

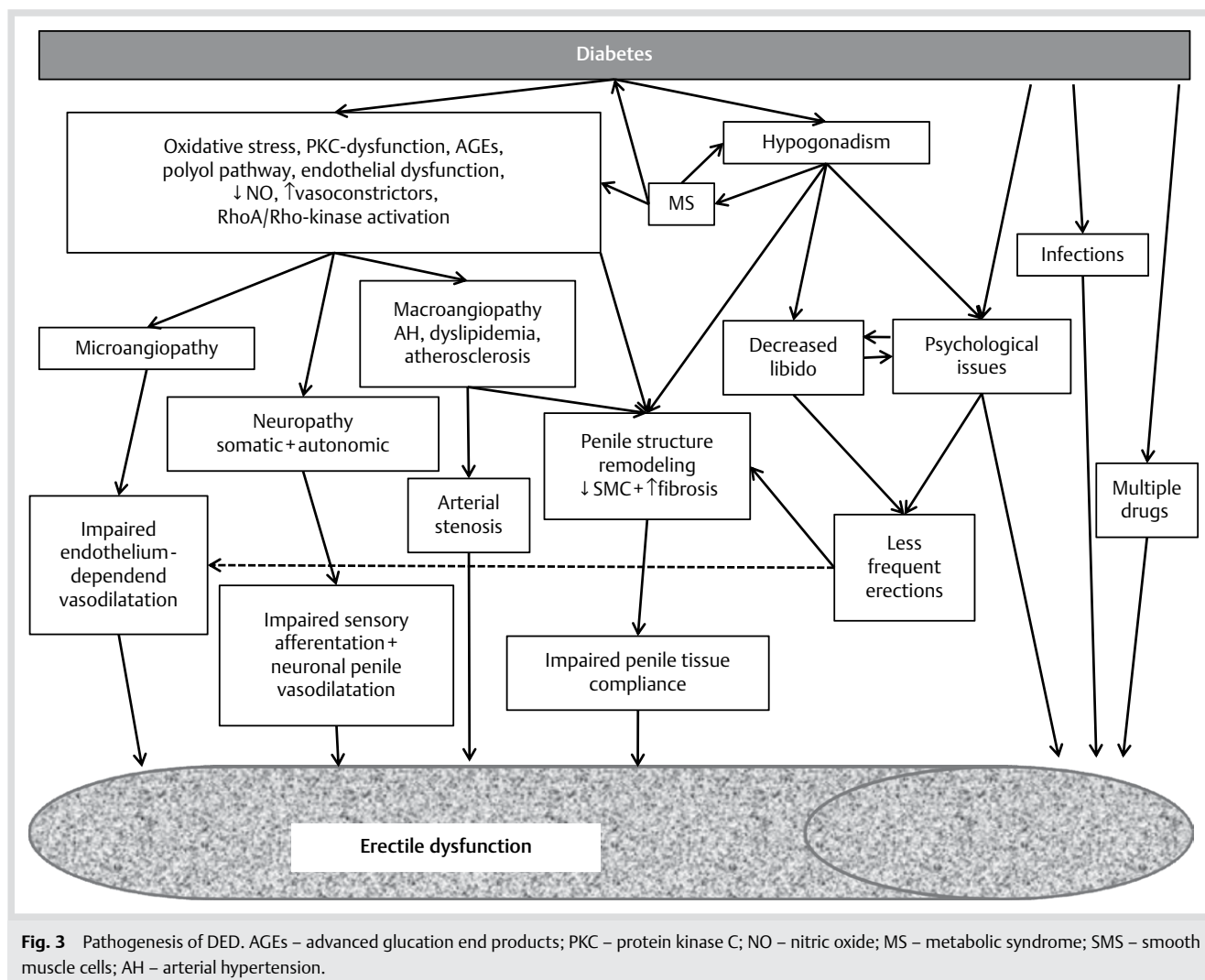


Fig. 3 Pathogenesis of DED. AGEs – advanced glycation end products; PKC – protein kinase C; NO – nitric oxide; MS – metabolic syndrome; SMS – smooth muscle cells; AH – arterial hypertension.

tion has been paid to the importance of DM as a vascular risk factor. It accelerates the development of endothelial dysfunction – an earlier event of vascular disease, induces oxidative stress and dyslipidemia, potentiates atherosclerotic process, aggravates arterial hypertension, etc. A vicious pathogenetic circle between DM and hypogonadism perpetuates – men with DM have lower levels of testosterone and men with hypogonadism have an increased risk of development of obesity, metabolic syndrome and DM with the full spectrum of their unfavorable cardiovascular consequences (Mulligan et al., 2006). This global vascular disorder takes place in the cavernosal bodies as well, where other more DM-specific pathogenetic biochemical mechanisms develop:

Endothelial dysfunction

This is probably the most discussed aspect of DED in the literature. Investigating the function of NO/cGMP signalling in human erectile tissues J. Angulo et al. (2010) used human corpus cavernosum (HCC) strips and penile resistance arteries (HPRA) collected from penile specimens from organ donors (OD) and from diabetic and non-diabetic men with ED undergoing penile prosthesis implantation (Angulo et al. (2010)). The relaxations to acetylcholine, electrical field stimulation, sodium nitroprusside, and sildenafil were evaluated in phenylephrine-contracted HCC and norepinephrine-contracted HPRA and cGMP content in HCC

was also determined. The impairment of endothelium-dependent relaxation in HCC and HPRA from ED patients was exacerbated by diabetes – E(max) 76.1, 62.9, and 49.3% in HCC and 73.1, 59.8, and 46.0% in HPRA from OD, non-diabetic and diabetic ED, respectively. Hypertension, hypercholesterolemia, or aging did not exert a further impairment of endothelial relaxation among ED patients. DM also caused a further impairment of neurogenic relaxation in HCC and HPRA. The basal and stimulated content of cGMP in HCC was significantly decreased in patients with ED, but specially reduced in diabetic patients. Diabetes clearly impaired PDE5 inhibitor-induced vasodilation of HPRA from ED patients. The authors concluded that ED is related to impaired vasodilation, reduced relaxant capacity, and diminished cGMP content in penile tissue. These alterations are more severe in diabetes and accompany reduced relaxant efficacy of PDE5 inhibition. Thus, an exacerbated reduction of NO/cGMP signalling could be responsible for ED in diabetic men and would explain their reduced response to treatment.

► **NO bioavailability** may be decreased by suppressed eNOS expression and/or activity or by increased NO scavenging. Jesmin et al. (2004) reported reduction of eNOS mRNA expression suggesting an eNOS deficient expression at transcriptional level in OLETF diabetic rats (Jesmin et al., 2003). In the same study decreased vascular endothelial growth factor (VEGF) expression and mRNA transcription in penile tissues

was also found. It should be mentioned that the Akt-dependent pathway mediates both shear stress and VEGF phosphorylation of eNOS (Musicki et al., 2004). The effects of VEGF include endothelial cell proliferation, migration, angiogenesis, and anti-apoptosis, increased eNOS phosphorylation and expression of anti-apoptotic proteins. There is strong evidence that VEGF is a survival factor for endothelial cells (Dimmeler, Zeiher, 2000). At the molecular level, VEGF can upregulate eNOS expression in endothelial cells (Papapetropoulos et al., 1997). Furthermore, increased expression of eNOS has been reported in the rat penis after intracavernosal injection with VEGF (Lin et al., 2002). These findings support the importance of VEGF as an eNOS inducer. It would be logical to assume that the reduced expression of eNOS shown by Jesmin et al. (2004) in the OLETF rat penis may be causally related to the decrease in VEGF expression in the tissue. Unlike eNOS, nNOS does not appear to be inducible by VEGF (Sheehy et al., 1997). The penile expression level of nNOS has been documented to remain unchanged in VEGF-treated rats (Lin et al., 2002). Thus, the VEGF-triggered biochemical events probably have no targets in the nNOS gene, which continues to produce nNOS transcripts at a steady level.

- ▶ **Oxidative stress** is a key pathogenic factor in the development of diabetic complications. Chronic hyperglycemia induces free radical (reactive oxygen species – ROS) production through formation of advanced glycation end-products (AGE), lipid peroxidation, polyol pathway activation, superoxide production, and the activation of protein kinase C. ROS participate in most studied mechanisms for the initiation and maintenance of functional and structural deterioration. Increased oxidative activity and the expression of inflammatory markers are seen in patients with DED. Circulating monocyte activity and expressions of inflammatory markers such as endothelin-1 (ET-1) and intracellular adhesion molecule-1 (ICAM-1) are used as markers for ROS and inflammation (Hidalgo-Tamola, Chitaley, 2009).
- ▶ **Advanced Glycation End-products (AGEs)**. Normally with aging every tissue in the body is glycated in some extent. In hyperglycemic conditions the glycation process is more active and leads to micro-structural changes on a molecular level, which can further compromise the function of the tissue and finally lead to macro-structural deterioration. AGEs bond covalently to the vascular collagen leading to thickening of the vascular wall, decreased elasticity, endothelial dysfunction and atherosclerosis (Bucala et al., 1991; Singh et al., 2001a). Interaction between AGEs and endothelial cells up-regulates adhesion molecules that mediate vascular damage. AGE also stimulates cytokine expression on monocytes and macrophages (Yan et al., 2008). AGEs are increased in corpora cavernosa of rats and men with DM and cause impaired cavernosal smooth muscle relaxation and ED in diabetic rats (Seftel et al., 1997; Cartledge et al., 2001b; Usta et al., 2003). One important mechanism for decreasing of cavernosal compliance and smooth muscle relaxation is through the generation of free radicals which react with NO and decrease its availability. Increased penile levels of ROS were found in diabetic rats. The resultant most reactive peroxynitrite is involved in cell damage and death. Summarizing, AGEs contribute to the development of DED by generating free radicals leading to oxidative cell damage and by quenching NO (Cartledge et al., 2001b; Bivalacqua et al., 2005; Khan et al., 2001).

- ▶ **Endothelins**. Endothelin has 3 isopeptides (1, 2 and 3) and 2 receptors bound to G-protein (ETA and ETB). ET-1 is a powerful vasoconstrictor released from the vascular endothelium in the penis Moore, Wang (2006). There is evidence that DED is related to a disturbed balance towards increased vasoconstriction, caused by endothelin and its receptors (Bivalacqua et al., 2003; Christ et al., 1995). The plasma levels of ET-1 are increased in diabetic men (Clozel et al., 1992). ETA-receptors are located on the SMC and induce vasoconstriction and cell proliferation. ETB-receptors are presented mostly on the vascular endothelium and induce vasodilatation through NO and prostacyclin release (Bivalacqua et al., 2003; Sima et al., 1996). On the contrary, these receptors mediate vasoconstriction in some arteries like coronary in dogs and mammary in men (Clozel et al., 1992; Teerlink et al., 1994). It was found that ETB-receptors are up-regulated in the cavernosal bodies of diabetic rabbits where it is supposed to have constrictive role. In this way an increase in ETB receptors and their ligands may cause disbalance and vasoconstriction (Sima et al., 1996). It is considered that the mitogenic effect of ETB causes early ultrastructural atherosclerotic changes in diabetics (Lu et al., 2004).
- ▶ **RhoA-Rho kinase**. RhoA is a GTP-binding protein affected by Rho-kinase. The ET1 induced vasoconstriction is related to the RhoA-Rho kinase pathway (Park et al., 2002; Wang et al., 2002; Buyukafsar, Un, 2003) the activation of which suppresses eNOS (Ming et al., 2002). Rho-kinase is found in the cavernosal tissue of rats, rabbits and men and is activated in diabetic rats. It is considered that the RhoA-Rho kinase pathway potentiates ED by the decreased production of NO in the penis (Rees et al., 2002; Bivalacqua et al., 2004; Chua et al., 2006).

Several other mechanisms have been described in which hyperglycemia leads to functional and structural changes in cavernosal bodies and arteries. The described complex pathogenetic attack decreases the capacity of SMC relaxation and functional dilatation of cavernosal structures, but also limits the penile arterial inflow through atherosclerotic changes.

Diabetic neuropathy (DN)

DN is the most common diabetic complication, affecting 10–90% of people with diabetes, depending of the diagnostic criteria and the age and duration of DM (Vinik et al., 1992; Young et al., 1993; Dyck et al., 1993; Tesfaye et al., 1996). Some studies showed an earlier development of DN in men, compared to women (Aaberg et al., 2008; Kamenov et al., 2010). Neuropathy is a very important pathogenetic factor in the development of DED. Because DN affects all levels of the neural system, disturbances could also happen on all levels in the complex process of erection – from the central initiation to the penis. In the literature much more attention is paid to the vascular aspects of DED compared to the neural ones (Kamenov, Traykov, 2012).

The *central aspects* of erection have been investigated in some studies, from fundamental investigations of sexual behavior to functional MRI imaging and PET in the phase of REM sleep, associated with nocturnal penile tumescences, as well as the whole sexual cycle in men (Nofzinger, 1997). It should be mentioned that central aspects of DN and DED have been much less investigated probably because of the insufficient options for diagnostic methods and selective therapeutic influence. Recently, MRI for structural (Frøkjær et al., 2013) and functional MRI for structural and functional changes and other methods have been used

for investigating the central aspects of DN (Selvarajah et al., 2014; Wilkinson et al., 2013).

In the clinical classification of DN traditionally DED is positioned in the genito-urinary autonomic DN. The initial stage of the erection process at penile level – NANC nerve endings nNOS activation and NO release has been shown to be impaired in animal models of DM1 and (although less convincingly) in DM2 (Hidalgo-Tamola, Chitale, 2009). Otsuka Long-Evans Tokushima fatty (OLETF) rats represent an appropriate model for spontaneously developed DM2 with its late complications (Kawano et al., 1992), including DN (Kamenov et al., 2006). OLETF rats showed decreased immunofluorescent staining for nNOS in dorsal nerves and 40% decrease in nNOS 160kDa protein expression relative to that of non-diabetic controls ($P < 0.01$), thus supporting an impaired nNOS effectiveness in DM2 (Jesmin et al., 2003). By applying different neurological tests it has been shown that diabetics with ED present more commonly with abnormal NCV, sphincter electromyography and vibration sensitivity compared to those without ED (Hakim, Goldstein, 1996; Hecht et al., 2001). The combination of sensory and autonomic disturbances leads to decreased sensory afferentation necessary for the initiation and maintenance of the erection, but also limits the effect of the critically necessary for the erection NO from the intracavernosal nerve terminals. In most studies no separate evaluation of the macro- and microvascular (including DN) complications is presented. We found that microangiopathy and in particular DN is a more important risk factor for DED than macroangiopathy (Kamenov et al., 2007). The presence of ED increased the likelihood to have macrovascular but in higher degree microvascular diabetic complications. These data support the crucial negative role of DN in the complex pathogenesis of DED and may explain why men with diabetes are more prone to ED compared to men with same degree of macrovascular disease but without DN.

Hypogonadism

is frequently associated with DM2 (Yagihashi et al., 2007; Bartolini et al., 2004; Corrales et al., 2004; Corona et al., 2007). There are strong causal links between the metabolic syndrome, ED and late onset hypogonadism. Even shortly after the diagnosis of DM2 the prevalence of hypogonadism (symptoms+TT < 3.2 ng/ml) is 17.6%, but only 0.2% of the subjects in this study reported occasional use of testosterone and none a current therapy of frequent use (Corona et al., 2014). Later-on in the evolution of the disease, in the average diabetic population, choosing a cut-off of total testosterone (TT) < 10.4 nmol/l for evaluation of 2165 men aged ≥ 45 years, visiting primary care practices in the United States, the investigators of HIM study reported that half of diabetic men were hypogonadal = 50.0% (45.5–54.4), OR(95%CI) = 2.09 (1.70–2.58) (Mulligan et al., 2006). Hypogonadism was also very common in other co-morbidities included in the metabolic syndrome: obesity = 52.4% (47.9–56.9); OR = 2.38 (1.93–2.93), arterial hypertension = 42.4% (39.6–45.2); 1.84 (1.53–2.22), hyperlipidemia = 40.4% (37.6–43.3); 1.47 (1.23–1.76) respectively. Many studies support the weight-increasing effect of hypogonadism and the testosterone lowering effect of obesity. It is difficult to answer which one is the initial event – hypogonadism or the metabolic syndrome. Even if the cause-consequence dilemma is still not definitely solved, the treatment should be directed to both problems.

Against the older opinion that testosterone is mostly a trigger of desire with limited importance for the lower levels of erection, a growing body of evidence supports its active participation and

importance on all levels of the above described hierarchic structure of the erectile process (Fig. 4).

On the cerebral level testosterone acts by itself, but also as its metabolites after appropriate enzymatic transformations to estradiol (via aromatase) and to dihydrotestosterone (via 5- α reductase). It stimulates the synthesis, storage and release of pro-erectogenic neurotransmitters and modulates the neuronal activity, receptor sensitivity, neurotransmitter liberation, the socio-sexual behavior (increasing libido) and positively influencing dopamine, NO, oxytocin, etc. On the spinal level testosterone activates the androgen-sensitive motoneurons of mm. bulbo- and ischiocavernosus and the androgen receptors in parasympathetic erectile area S₂₋₄.

It is generally accepted that androgens are critical for the development, growth, and maintenance of penile erectile tissue. Animal studies showed testosterone dependency of the eNOS-containing cavernosae parasympathetic fibers (Baba et al., 2000). In animal models, androgen deprivation produces penile tissue atrophy concomitant with alterations in dorsal nerve structure, endothelial morphology, reduction in trabecular smooth muscle content, and an increased deposition of extracellular matrix. Further, androgen deprivation results in the accumulation of adipocytes in the subtunical region of the corpus cavernosum (Traish, Kim, 2005). Testosterone deprivation is followed by the programmed cell death of cavernosal SMC (Porst, 2007). Interestingly, testosterone stimulates both the initiator of the erection (NOS) and its terminator (PDE-5), thus fine balancing the whole process. Androgen deficiency diminishes protein expression and the enzymatic activity of nitric oxide synthases (eNOS and nNOS) and PDE-5. The androgen-dependent loss of erectile response is restored by androgen administration but not by administration of PDE-5 inhibitors alone. These data suggest that androgens regulate trabecular smooth muscle growth and connective tissue protein synthesis in the corpus cavernosum. Further, androgens may stimulate the differentiation of progenitor cells into SMC and inhibit their differentiation into adipocytes. Clinical and preclinical studies have suggested that venoocclusion is modulated by the tone of the vascular smooth muscle of the resistance arteries and the cavernosal tissue and a balance between trabecular smooth muscle content and connective tissue matrix. In men with ED, venous leakage is thought to be a common condition among non-responders to medical management and is attributed to penile smooth muscle atrophy. Summarizing, Traish and Kim (2005) concluded that androgens

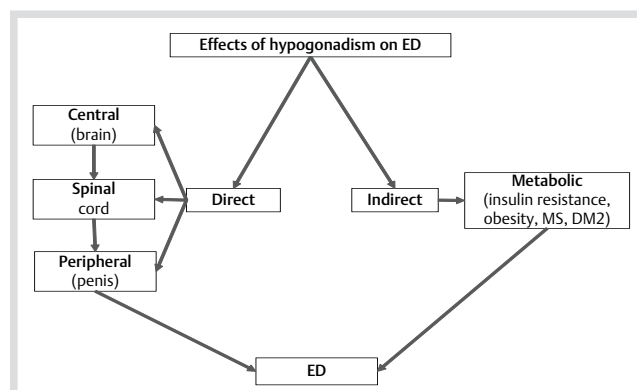


Fig. 4 Effects of hypogonadism on ED. MS – metabolic syndrome; DM2 – diabetes type 2; ED – erectile dysfunction. (modified from Kamenov, Frederique Courtois 2013).

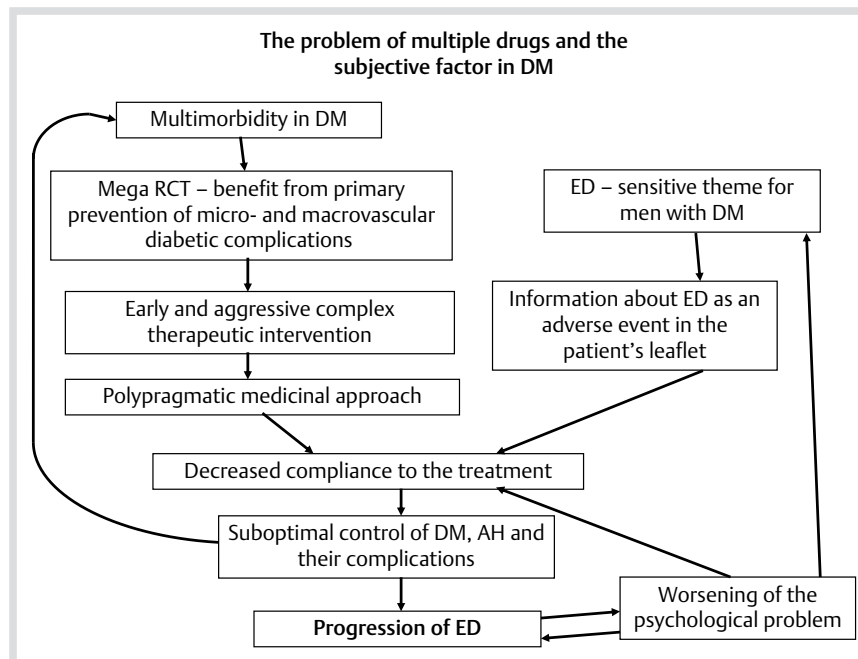


Fig. 5 The problem of multiple drugs and the subjective factor in DM. RCT – randomized controlled trials; DM – diabetes mellitus; AH – arterial hypertension (modified from Kamenov, 2013).

exert a direct effect on penile tissue to maintain EF and that androgen-deficiency produces a metabolic and structural imbalance in the corpus cavernosum, resulting in venous leakage and erectile dysfunction (Traish and Kim (2005)). The testosterone level necessary for normal EF still needs exact determination. Interventional studies in men have demonstrated the favorable effect of testosterone replacement therapy (TRT) on EF in men with organic hypogonadism, mostly in cases when it is the only reason for ED (Shabsigh, 2006). Other structural changes related to DM include the loss of normal cavernosal endothelium and SMC (Burchardt et al., 2000) and an increased deposition of collagen and thickening of the basal lamina leading to fibrosis (Jevtich et al., 1990).

Other Sexual Dysfunctions

DM is associated not only with ED but with all aspects of sexual dysfunction – sexual drive, ejaculatory function, sexual problems, sexual satisfaction, etc. (Burke et al., 2007). In patients with DM there is a strong association between ED and reduced libido (OR=4.38, 95% CI=1.39–13.82) and an even stronger one between ED and premature ejaculation (PE)=4.41 (2.08–9.39) respectively. The presence of one of these 3 conditions (ED, PE and reduced libido) requires screening for the other 2 (Malavive et al., 2008). Corona et al. (2014) found PE, delayed ejaculation, and hypoactive sexual desire in 28.3, 32.9, and 58.4%, respectively in men around the diagnosis of DM2 (Corona et al. 2014). A study from Minnesota demonstrated DM to be associated with decreased sexual desire, ejaculatory function and sexual satisfaction (Burke et al., 2006). Another study reported 80% of the interviewees to have sexual problems – decreased libido (50.3%), PE (19.7%), retrograde ejaculation (19.2%). According to the answer to the question for having problems with the erection it appeared 51.5% had ED and, according to IIEF, 87.9% (Adegite et al., 2009). The sexual problem preceded the diagnosis of diabetes in 30.2%. In 45.3% of cases no medical consultation has been sought.

Balanitis is more common in diabetes (16%) compared to general population (5.8%) (Fakjian et al., 1990). It has been shown that 12% of men have had balanitis during the last 2 years before the diagnosis of DM (Drivsholm et al., 2005). Inflammation, pain and discharge, related to mycotic balanitis may have somatic and psychological unfavorable effects on the erection and sexual intercourse. **Phymosis**, a condition where the foreskin cannot be fully retracted over the glans penis, is common in diabetes – 32% of men admitted to a urological clinic with phymosis have had DM (Drivsholm et al., 2005). Phymosis may cause pain and difficulties in physical and psychological aspects during coitus. **Peyronie disease** (induratio penis plastica) represents a usually painful connective tissue disorder with abnormal curvature of the penis when erect due to chronic inflammation of the tunica albuginea, forming cord-like fibrous plaques from hardened scar tissue. Although a variety of treatments has been used none have been especially effective. It is associated with DM (El-Sakka, Tayeb, 2005) and correlates with its duration (Arafa et al., 2007). The prevalence in diabetic men varies from 8.1 to 18.3% (El-Sakka, Tayeb 2005; Schwarzer et al., 2001; Tefekli et al., 2006). In patients with DED prevalence of 20.3% (Arafa et al., 2007) has been reported and 16 (Kadioglu et al., 2004) compared to 3.2% (Schwarzer et al., 2001) and 3.64% (Rhoden et al., 2001) in non-selected populations.

DM is a disease, usually accompanied by several co-morbidities. The last clinical mega-trials recommended an early and aggressive therapeutic intervention aiming at primary prevention of micro- and macrovascular diabetic complications. The polypragmatic medication approach is typical in patients with DM (Fig. 5). Many of the used **drugs** (antihypertensive, SSRI, neuropathic pain control, etc.) are claimed to have an unfavorable effect on EF. Men with DM are psychologically more sensitive and focused on the subject of ED. In many cases the information about possible ED as an adverse event of the particular medication read in the patient information leaflet, may compromise the understanding of the necessity for keeping normal blood sugar, lipids and blood pressure levels, interfering in this way with compliance and adherence to the treatment. This imposes a careful selection of the treatment options choosing a *harmo-*

nized therapeutic scheme aiming at no between-drug interference but also no unfavorable effects on different aspects of the metabolic syndrome and ED in patients with DM.

Diagnostic Process

The diagnostic process in DED does not differ significantly from the usually described diagnostic algorithms for ED. The clinical workout for ED could be divided in 2 steps: (1) *diagnosis* – confirmation of the presence of ED and (2) *differential diagnosis* – identification of all possible factors and causes for the development of the particular ED. The second step is very important for the treatment decision for all treatable pathogenetic factors (◉ Table 1).

1. The **diagnosis of ED** is not a difficult one, but may be impeded by several mainly subjective obstacles. Men are usually distressed by the disease and ED and are ashamed to speak voluntarily about the problem (◉ Fig. 6). Medical specialists with a general medical profile do not initiate this conversation as well because of lack of knowledge, interest, motivation or time. Consultation in this sensitive area needs special skills and practice in the field of sexual medicine – an interdisciplinary specialty with a growing number of experts. Several validated questionnaires may be used for the diagnosis of ED. *The International Index of Erectile Function (IIEF)* (Rosen et al., 1997) is currently the most widely used questionnaire (Basu,

Ryder, 2004). Commonly, the domain for EF is preferred including questions 1–5 and 15 addressing the last 4 week period. The presence of ED is assumed if the score is less than 26 points. ED is stratified into severe <11, moderate <16, moderate to mild <21 and mild ≤25 points. *Sexual Encounter Profile Question-2 (SEP2)* – have you been able to insert your penis into your partner's vagina? *Sexual Encounter Profile Question-3 (SEP3)* – Was your erection long enough to allow successful sexual encounter? *Global Assessment Question (GAQ)* – Do you think that the treatment improved your erection? (answer yes/no). This question is asked after the use of the drug.

2. The **differential diagnosis** is based on carefully collected patient history which may help significantly the orientation for the main causes of the ED in the particular case.

- ▶ In DM the origin for ED is organic in most cases but it should not be forgotten that in young men with diabetes with shorter duration psychogenic component may prevail. It should be remembered that **psychogenic aspects** are present in different degree in all patients independent of the stage of the disease. When further psychological support and therapy is planned, the patient is best referred to the appropriate specialist.
- ▶ Patients with DED need more common **vascular investigations** with Doppler for diagnostic reasons and therapeutic options.
- ▶ More sophisticated investigations like RigiScan – a device for ambulatory monitoring of the spontaneous **nocturnal tumescences** usually 3–5 times during the night, typically during REM sleep, based on evaluation of 2 circumferent pneumatic sensors placed around the penis during the night, might be helpful on some occasions. The simple stamp-test could also be used if doubt exists about nocturnal tumescences. The pharmacological test with intracavernosal injections of vasoactive drugs and Doppler evaluation of the pre- and post-application bloodflow, with or without visual sexual stimulation, is usually performed in the medical office.

Table 1 Main symptoms and signs of Late onset hypogonadism (LOH) in men.

Somatic	Psychologic
↑ fat mass (especially visceral)	↑ irritability and depressiveness
↓ free fat mass	↓ energy
↓ muscle mass, strength and endurance	↓ libido and erections (ED)
↓ bone mineral density	↓ cognitive functions
↓ hair growth and skin thickness	↓ quality of sleep

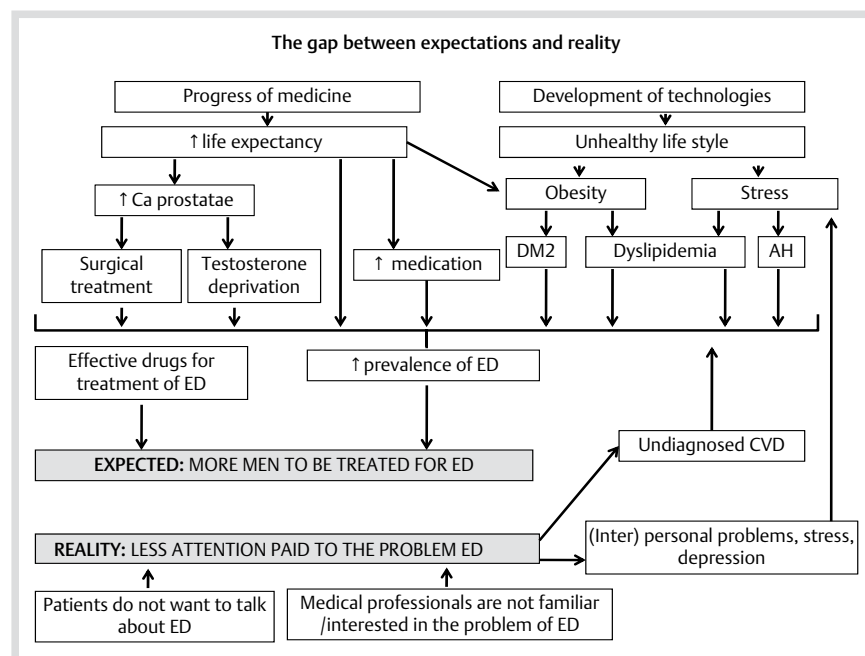


Fig. 6 The gap between expectations and reality. (modified from Kamenov, 2013).

- ▶ **Neurologically** focused history and tests are of special interest in DED. It should be mentioned that the absence of neurological symptoms and signs does not necessarily mean the absence of DN. On the contrary, some symptoms and signs caused by other neurological diseases are commonly attributed to DN because medical specialists are expecting the patient to have this diabetic complication. DN is a diagnosis *per exclusionem*. The most common initial nerve damage usually affects different sensory modalities and autonomic functions. Simple sensory diagnostic devices may be applied for evaluation of sensory function like the 128-Hz Rydel-Seiffer tuning fork (vibration perception), Semmes-Weinstein 5.07 (10g) monofilament (pressure perception), thermal discriminator (thermal perception), etc., as well as autonomic tests (Neuropad for sudomotor function). They could be easily used in the everyday clinical practice in the community for the improvement of diagnostic sensitivity (Kamenov et al., 2010; Kamenov, Traykov, 2012b; Manes et al., 2014). Special neurological tests may also be necessary in patients with ED (Diemont, Meuleman, 1997).
- ▶ The reported very high prevalence of low **testosterone** (T) levels in diabetic men makes the exclusion of hypogonadism a more important initial diagnostic step compared to non-diabetic men. Omitting T determination at this point of the evaluation of DED may cause further ineffectiveness of pro-erectogenic medications, loss of confidence and disappointment and worsening of the treatment prognosis and increasing frustration. Early morning total T levels below 8 nmol/L, confirmed on a consecutive visit, associated with corresponding symptoms (● **Table 1**) usually require testosterone supplementation after exclusion of the respective contraindications. Levels above 12 nmol/L usually are not considered as an indication for TRT. If the patient has total T levels in the grey zone (8–12 nmol/L) the case needs further evaluation and determination of free T. In detail the diagnostic approach for hypogonadism is described elsewhere (Wang et al., 2009). It should not be forgotten that decrease of T might be caused by different endocrine (hypothalamic, pituitary, testicular, etc.) and other diseases and drugs, which makes the full set of differential diagnosis for hypogonadism necessary. Prolactinomas and other pituitary or hypothalamic tumors in men cause typically hypogonadotropic hypogonadism and because of the oligosymptomatic presentation are commonly diagnosed at the advanced stage of macrotumors. A common cause for hypogonadism is obstructive sleep apnoea. The diagnosis is suspected from the history and questionnaires for night apnoea periods and daily sleepiness, and confirmed by polysomnography. Treatment with mechanical devices (CPAP, BPAP) leads to improvement of metabolic, hormonal, sexual, and QoL indices (Reinhardt et al., 2004). Haemochromatosis is one of the most common genetic disorders with homozygote frequency of 0.3–0.5% and a carrier frequency of 6.7–10% (Gluckman 1996). It may cause DM and hypogonadism with primary (testicular involvement), secondary (pituitary), tertiary (hypothalamus) origin or a combination of them. Treatment, particularly at the earlier stages, may improve the hormonal problems (Siemons & Mahler 1987; Angelopoulos et al., 2007).

Treatment Options for DED



The already described mixed pathogenesis of DED requires a complex treatment which can be divided into general and specific measures.

The **general measures** include the improvement and control of the main pathogenetic factors leading to DED. The therapeutic approach does not differ from the currently accepted options for reaching the appropriate for the particular patient targets for blood glucose, lipids and blood pressure control as well as the cessation or limitation of unhealthy lifestyle habits like smoking, alcohol overconsumption, immobilization, stress, use of recreational drugs, etc.

Although the data about the beneficial effect of *life style modification* on ED are limited diet and physical activity changes should always be recommended for diabetic men with ED (Giugliano et al., 2010). Nevertheless studies investigating the effect of *weight loss* on DED are scarce (Stoian et al., 2014). The Look AHEAD (Action for Health in Diabetes) trial examined 1-year changes in EF, measured by the IIEF in 372 overweight/obese men aged 45–74 with DM2 randomly assigned to diabetes support and education or to intensive lifestyle intervention involving group and individual sessions to reduce weight and increase physical activity. At 1 year, the intensive group lost a greater percent of initial body weight (9.9 vs. 0.6%), had greater improvements in fitness (22.7 vs. 4.6%) and EF improved more (17.3±7.6 at baseline; 18.6±8.1 at 1 year) than the control group (18.3±7.6 at baseline; 18.4±8.0 at 1 year); $P=0.04$ and after adjusting for baseline differences $P=0.06$. According to the results of the 82% of men who finished the study the authors concluded that in this sample of older overweight/obese diabetic men, weight loss intervention was mildly helpful in maintaining EF (Wing et al., 2010).

Strict *glycemic control* is the cornerstone in the treatment of DM and prevention of its complications like DED. Poor control increases the risk for ED 2–5-fold compared to good control (Fedele et al., 1998; Klein et al., 2005). C-C. Lu et al., (2009) concluded in a study including 792 subjects with 83.6% of them having ED and 43.2% – severe ED that better glycemic control probably would reduce the prevalence of ED and its severity among the younger men with DM2, but aging is the major determinant for ED risk for the older group (Lu et al., 2009). Although new options are proposed (Hidmark et al., 2014), until now the results of pathogenetic treatment of DN have been generally disappointing, most probably because of the late initiation of the treatment. There are some exceptions from this non-optimistic conclusion like alpha-lipoic acid (review in Ziegler 2006; Boulton et al., 2013), and benfothiamine (Stracke et al., 2008).

The **specific measures** include the psychotherapy, oral treatment, intracavernosal injections and intraurethral application of PgE1, vacuum constrictor devices and penile implants. Summarizing the results in the literature it should be mentioned that:

1. There are not many studies designed with focus on diabetic patients. Usually diabetics are sub-groups of larger patient populations. In some trials DM is even an exclusion criterion.
2. In most series diabetes (type, duration, control, etc.) and its macro- and microangiopathic complications including DN (presence, stage and treatment) are not described in detail.
3. In most cases oral treatment should be applied in the highest dose – sildenafil 100 mg, vardenafil 20 mg, tadalafil 20 mg, avanafil 200 mg, udenafil 200 mg, mirodenafil 100 mg.

4. The effectiveness of the treatment in diabetic men is lower compared to non-diabetic (Price, Hackett, 2008). This difference is even underestimated because commonly poor glycaemic control is an exclusion criterion at enrollment in the randomized clinical trials (RCT).
5. Patients with DED require more often switching to a higher line of treatment like intracavernosal injections, vacuum constrictor devices and implants, compared to healthy men.
6. Vascular reconstruction operations for ED are very rarely performed in diabetic patients.

Psychological aspects of ED in DM

Although there is a growing number of studies on the association between DED and psychological factors, the dominant scientific interest is focused on the organic pathology of DED. Some authors draw attention to the individual and marital pathology in diabetic men and the significance of psychological dimensions on the sexual impact of this illness (Siddiqui et al., 2012). ED is associated with higher levels of diabetes-specific health distress and worse psychological adaptation to DM, which in turn worsens metabolic control (Berardis et al., 2002). Diabetic men are more likely to consider their ED to be severe and permanent, compared with non-diabetic (Eardley et al., 2007). ED contributes to poorer overall quality of life in diabetic patients (Avasthi et al., 2011)

PDE-5 inhibitors

A new era in "erectology" began about 15 years ago with the introduction of the first inhibitor of PDE-5 – sildenafil. The members of this group of drugs inhibit the main PDE isoform in the cavernosal smooth muscle – type 5 responsible for the degradation of cGMP (Wallis et al., 1999) whose level increases and leads to improvement of the erection. Later PDE-5 inhibitors – vardenafil, tadalafil and avanafil – have higher specificity to the target iso-enzyme (Saenz de Tejada et al., 2001a). Further avanafil and udenafil were also introduced on the market. Currently available PDE-5 inhibitors are very effective and safe and represent the first line therapy for treatment of ED, including DED, although less effective in diabetic men (Ng et al., 2002; Padmanathan, 2003; Goldstein et al., 2003). Only 56% of DM2 patients respond to PDE5, compared to 87% response in normal patients (Rendell et al., 1999). Even when a good response to treatment has been reported initially in DM2 patients, the effect is not sustainable overtime. After 1 year of treatment of men with DED, IIEF scores reverted to baseline values (Penson et al., 2003).

Sildenafil

Sildenafil is the most studied PDE-5i with an enormous data base. It has been successfully used in doses 25, 50 and 100 mg in the general population as well as in difficult-to-treat subgroups, particularly in DED. In one of the first trials – multicenter, randomized, double-blind, placebo-controlled study (RCT) 268 men with DED were randomized to sildenafil in a flexible escalating dose or placebo for a period of 12 weeks. In the active arm 56% of the patients had improvement of erections compared to 10% on placebo (Rendell et al., 1999).

Sildenafil has also been shown to be effective vs. placebo in DM1 patients. Significant improvements in the ability to achieve erections evaluated by IIEF (35.7 vs. 19.9%) and to maintain erections (68.4 vs. 26.5%), improved erections with treatment (GAQ 66.6 vs. 28.6%), and successful attempts at intercourse (63 vs. 33%) were reported (Stuckey et al., 2003).

In a RCT a total of 282 men were randomized to fixed-dose sildenafil or placebo. A significant improvement from baseline in IIEF Q3 (55 vs. 29%) and IIEF Q4 (61 vs. 25%) lead to the conclusion that sildenafil is a moderately effective treatment for ED in men with diabetes. The response rate was lower and cardiovascular events were higher than previously reported in non-diabetic patients (Safarinejad, 2004).

Sildenafil has been investigated for potential benefits in different diabetic areas. After one dose of 50 mg an improvement of cerebrovascular reactivity, assessed using breath holding-hyperventilation test with trans-temporal ultrasound examination on the middle cerebral artery, was observed in diabetic, but not in non-diabetic men (Al-Amran et al., 2012). A. Burnett et al. (2009) evaluated the changes of biomarkers of vascular function serum cGMP, 8-isoprostane, IL-6 and IL-8 in men with DM2 with ED after use of sildenafil for 12 weeks (Burnett et al., 2009). They concluded that short-term continuous sildenafil treatment causes improvement in systemic endothelial function remaining for a period after its discontinuation. However, they did not mention any influence of this treatment on systemic oxidative stress or inflammation, or a long-term beneficial effect on EF. Grover-Páez et al. (2007) determined the levels of hs-CRP, microalbuminuria, homocysteine, HbA1c and EF at baseline and after 30 days sildenafil 50 mg daily or placebo. Men on sildenafil had a significant decrease of microalbuminuria vs. baseline ($p < 0.01$) and vs. placebo ($p < 0.02$) and of HbA1c ($p < 0.01$ and $p < 0.01$ respectively) (Grover-Páez et al., 2007). To evaluate the endothelial function 24 DM2 men were randomized to daily sildenafil 50 mg or placebo for 10 weeks. At the end of the trial, those who received sildenafil had significantly improved erectile rigidity as captured by IIEF-5 ($p < 0.001$) and increased endothelial function via brachial artery flow-mediated dilation ($p < 0.01$) (Deyoung et al., 2012).

Tadalafil

Tadalafil is an effective drug for treatment of ED of different severity and etiology. The most important difference compared to other available currently approved PDE-5 inhibitors is its long half-life (17.5) hours allowing (1) a long-lasting clinical effect of 36 h by on demand dosing with 5, 10 or 20 mg, and (2) full diurnal therapeutic coverage by daily use in lesser dose (2.5 and 5 mg). Besides the evidence in the general population (Brock et al., 2002; Carson et al., 2004) the drug has been successfully used in difficult-to-treat patients with severe organic ED (Carson et al., 2005), DED (Saenz de Tejada et al., 2002; Fonseca et al., 2004), after radical prostatectomy (Carson et al., 2005; Montorsi et al., 2004) or radiation therapy (Incrocci et al., 2007). Tadalafil 10 and 20 mg on demand resulted in 56 and 64% improvement of the erections compared to 25% in the placebo arm in a study with 191 diabetic men (Saenz de Tejada et al., 2002). Based on the significant benefit of low dose daily tadalafil (McMahon, 2004; Porst et al., 2008) the FDA approved this regimen in 2008. Tadalafil 5 mg once daily is used also for lower urinary tract symptoms suggestive of benign prostatic hyperplasia (Porst et al., 2013).

In the diabetic arm (726 men with DED with minimal duration of 3 months) of the randomized crossover, open study with 4262 patients from 392 centers in 14 European countries The Scheduled Use vs. on-demand Regimen Evaluation (SURE) study tadalafil 20 mg was used regularly 3 times a week irrespective of sexual activity or on demand (Buvat J et al., 2006). The patients were divided into 2 groups according to the used regimen and

after a 5–6 weeks period the 2 arms were crossed using the alternative dose regimen for the same period of time. Regarding DM, patients were considered having type 1 or 2 according to current insulin use and the age of onset of DM – before or after 40 years of age with no pre-selection for diabetic complications. At the end point on both regimens, the mean IIEF EF domain score was 22, and >40% of the patients had a normal EF domain score (≥ 26). The proportion of “yes” responses was $\geq 73\%$ for SEP2 (penetration), $\geq 58\%$ for SEP3 (successful intercourse), $>46\%$ for SEP4 (hardness of erection), and $\geq 45\%$ for SEP5 (overall satisfaction). Efficacy was maintained up to 36h post-dosing. More than 70% of sexual attempts while on the 3-times-per-week regimen and approximately 50% of the attempts with on-demand treatment occurred >4 h post-dosing. Treatment preference was 57.2% for on demand and 42.8% for 3 times per week. The authors concluded that tadalafil, when taken on demand or 3 times per week, is efficacious and safe in men with DED.

Schulman et al. (2004) studied the differences in effectiveness of the fixed dose tadalafil over time (Schulman et al., 2004). They combined the data from five 12-week RCTs including 3 groups of 308, 321 and 258 men on placebo, 10 and 20 mg tadalafil respectively. The very first dose lead to significant improvement of SEP2 – 47, 74, 79%; SEP3 – 31, 56, 67% and SEP5 (satisfied overall with their sexual experience) – 15, 36, 47% respectively. Later on the effect increased reaching a plateau of 95% (SEP2), 90% (SEP3), and 81% (SEP5) between the 4th and 8th dose.

In a meta-analysis of 12 RCTs with tadalafil Fonseca et al. (2004) included 637 men of mean age 57 years with DM and mean baseline IIEF 12.6 (Fonseca et al., 2004). The use of tadalafil 10 or 20 mg lead to an improvement of 7.4 points vs. 0.9 points in the placebo group. In men with DM 53% of the sexual attempts were successful vs. 22% in the placebo group. Baseline IIEF showed a negative correlation with HbA1c, but the response to tadalafil treatment was not related to the glycemic control, type of treatment or previous use of sildenafil. No analysis was made on the pathogenic factors for ED. Comparison of this population with 1 681 men of mean age 56 years with ED (baseline IIEF=15) without diabetes demonstrated more severe ED in DM but independently equal therapeutic effect to tadalafil.

Vardenafil

Vardenafil is a powerful PDE5 inhibitor whose efficacy and tolerability at doses 5, 10 and 20 mg were shown in RCTs including large populations of men with ED (Porst et al., 2001; Hellstrom et al., 2002; Hatzichristou et al., 2004), and men presenting difficult-to-treat groups like DM, after prostatectomy etc. (Goldstein et al., 2003; Brock et al., 2003). The reliability of vardenafil was determined in a retrospective analysis of 2 clinical studies showing an increased probability for penetration, maintenance of erection and higher general satisfaction compared to placebo. Most of the patients who responded to the first dose of vardenafil reported success during the whole 12-week treatment period (Montorsi et al., 2004). In one open study with 398 non-preselected men the efficacy and tolerability of vardenafil used at initial dose of 10 mg and titrated to 5 or 20 mg were investigated (Potempa et al., 2004). At the end of the 10-week therapeutic period an improvement in EF domain of IIEF from 13.9 to 25.9 points, successful penetration SEP2 in 89%, maintenance of erection SEP3 in 78% and general satisfaction of the treatment (GAQ) in 92% were reported.

Goldstein et al. (2003) conducted in the USA and Canada a multicenter RCT with 452 men with DM1 and DM2 with HbA1c $< 12\%$ (Goldstein et al., 2003). Patients were randomized in 3 groups – vardenafil 10 or 20 mg or placebo over a 12 week period. The drug was taken 1 h before intercourse no more than once a day. After the end of this period the patients received 10 or 20 mg vardenafil for another 12 weeks. Treatment efficacy was assessed using IIEF, GAQ, SEP2 and SEP3. Sub-analyses of the data was made according to the baseline severity of ED, HbA1c (< 6 , < 8 and $> 8\%$), and dose-response effect. Special focus was placed on the registration of possible side effects. At the end of the trial for the different doses vardenafil 57 and 72% of the men reported an improvement in EF according to GAQ compared to 13% improvement in the placebo group. On the twelfth treatment week IIEF increased by 19.0 points. Successful penetration (SEP2) was achieved by 64%, and successful coitus (SEP3) by 54% of men. The results of this study were summarized in 3 major conclusions: (1) Vardenafil has a favorable dose-dependent treatment profile on DED. (2) The efficacy of vardenafil is present irrespective of the baseline severity of ED and glycemia. (3) The drug has no serious side effects and has very good tolerability. No disturbances of color vision were reported.

Patient satisfaction with the treatment for ED is critical for his long term compliance (Dean et al., 2006). In one international trial with 3 291 men with ED 47% of them pointed the “constant efficacy” as the most important feature of the treatment (Eardley et al., 2003; Meuleman et al., 2003). This is extremely important in men with DM, who report their ED to be severe and permanent, seek medical help more often and are more prone to discontinuation of the treatment because of an unsatisfactory result, than are men without diabetes (Eardley et al., 2007). Most of the above mentioned research suggests that responsiveness to PDE5i drugs increases with sequential dosing from initiation; 8 doses are generally considered an adequate trial of therapy to establish efficacy. The effect of the first intake of a PDE5 inhibitor is a prognostic factor for its treatment efficacy. It can be stated that the initial success and further reliability of the treatment for ED are crucial for patient satisfaction with the treatment that directly affects compliance. L.Valiquette et al. (2005) evaluated the efficacy of the first intake of 10 mg vardenafil vs. placebo in non-selected population of 600 men of mean age 54 ± 11 years (20–79), of whom 30% had hypertension, 15% DM and 16% dyslipidemia (Valiquette et al. (2005)). Baseline EF domain of IIEF is 14.6 ± 5 points, and ED duration about 5.6 ± 5.2 years. Efficacy regarding SEP2 is $87\% = 520$ of total 600 men reported successful penetration and 85% of them maintained their erection to the end of the intercourse (SEP3), which equals the 74% success of the first intake of vardenafil regarding SEP3 in the general population. Although head-to-head comparisons are scarce the data about the effectiveness of the PDE-5 inhibitors in diabetic men suggest a similar degree. Recently, we compared the effect of the first intake of tadalafil 20 mg and vardenafil 20 mg in men from the difficult-to-treat group with DED and proven DN (Kamenov, 2011). To synchronize the therapeutic windows, sexual intercourse should have been initiated in the interval of 1–6h after the drug intake. In this time frame the effectiveness (IIEF-EF, SEP2, SEP3, GAQ) of both medications was comparable.

Avanafil

Avanafil was recently approved by the US Food and Drug Administration (2012) and European Medicine Agency (2013) for the management of ED. It was studied in over 1 300 patients during

clinical trials, including patients with DM and those who had undergone radical prostatectomy, and was found to be more effective than placebo in all men who were randomized to the drug. The medication was studied with on-demand dosing as 50, 100, or 200 mg that may occur after food and/or alcohol. Avanafil has a very quick onset of action and higher specificity for phosphodiesterase type 5 vs. other phosphodiesterase subtypes (Burke, Evans, 2012).

In a 12-week, multicenter RCT 390 men with DED were randomized 1:1:1 to receive avanafil 100 or 200 mg, or placebo. Compared with placebo IIEF-EF domain, SEP2 and SEP 3 improved with both doses avanafil – 100 mg ($P \leq 0.002$), and 200 mg ($P < 0.001$). The authors concluded that avanafil was safe and effective for treating ED in men with diabetes and was effective as early as 15 min and more than 6 h after dosing. The adverse events seen with avanafil were similar to those seen with other PDE-5 inhibitors (Goldstein et al., 2012).

In a 52-week open-label extension phase of two 12-week RCTs 686 patients with mild to severe ED with or without diabetes were assigned to avanafil 100 mg, but could request 200 mg (for increased efficacy; 100/200-mg group) or 50 mg (for improved tolerability). SEP2 and SEP3 success rates improved from 44 to 83% and from 13 to 68% (100-mg group) and from 43 to 79% and from 11 to 66% (100/200-mg group), respectively. Mean IIEF-EF domain scores improved from 13.6 to 22.2 (100-mg group) and from 11.9 to 22.7 (100/200-mg group). Based on the the long-term tolerability and improvement in sexual function, coupled with rapid onset, the authors concluded that avanafil is well suited for the on-demand treatment of ED (Belkoff et al., 2013).

Recently, Yilmaz et al. (2014) injected intracavernosally 1 μ M avanafil for 10 weeks in rats with streptozotocin induced diabetes. Avanafil partially restored the diminished intracavernosal pressure responses in diabetic rats. After the application of different stimuli on corpus cavernosal strips from the diabetic group the relaxation responses were enhanced and contractile responses diminished. The authors suggested that intracavernosal administration of avanafil might also be beneficial for the treatment of ED in patients with DM2 (Yilmaz et al., 2014).

Udenafil

Udenafil is a potent novel PDE-5 inhibitor approved for use in Korea. Udenafil has a T_{max} of 1.0–1.5 h and a $T_{1/2}$ of 11–13 h. Therefore, both on-demand and once-daily use of udenafil have been reported. Udenafil's efficacy and tolerability in doses 100 or 200 mg have been evaluated in several studies, and recent and continuing studies have demonstrated udenafil's promise in both dosing regimens. Presently, tadalafil is the only FDA-approved drug for daily dosing, but udenafil can be used as a once-daily dose for erectile dysfunction patients who cannot tolerate tadalafil due to phosphodiesterase subtype selectivity (Kang, kim, 2013). Recently Park et al. (2014) proved the equal efficacy and safety of 200 mg on-demand or 50 mg once-daily dosing udenafil for 8 weeks on IIEF, SEP Q2 and Q3, GAQ, and vascular endothelial markers in a multi-center, randomized, open-label, parallel-group, 12-week study with 161 DM2 patients. The authors concluded that both regimens were well-tolerated with flushing and headache being the most frequent adverse events and further studies are needed to assess the effect of daily udenafil treatment in diabetic patients (Park et al. (2014)).

Udenafil as an on-demand or once-daily dose is effective and tolerable, but more studies are needed in patients of other ethnicities and with comorbid conditions such as DM, hypertension, and benign prostate hyperplasia (Kang, Kim, 2013).

In a multicenter, fixed-dose RCT with 174 Korean patients with DED randomized to placebo, 100 or 200 mg of udenafil for 12 weeks were evaluated by IIEF (Q3 and Q4), the rate of achieving normal EF (IIEF ≥ 26), SEP2, SEP3, and GAQ. Compared with the placebo, patients receiving both doses of udenafil showed statistically significant improvements in the IIEF-EFD score. However, a statistically significant difference was not observed between the udenafil 100 and 200 mg groups. Similar results were observed in the comparison of Q3 and Q4 of IIEF, SEP diary, and GAQ. The percentages of subjects experiencing at least one adverse event related to the study drugs were 3.6, 15.8, and 22.4% for the placebo, udenafil 100 and 200 mg groups, respectively. Major adverse events were flushing, headache, nausea, and conjunctival hyperemia. The study concluded that udenafil was significantly effective for the treatment of ED, demonstrating significant improvement in EF in patients with DM. The incidence of adverse events was relatively low and well tolerated in patients with DM (Moon du et al., 2011).

Mirodenafil

A multicenter, parallel-group, fixed-dose RCT was conducted with 112 subjects who were randomized to either placebo or mirodenafil 100 mg on demand for 12 weeks. The active group showed significantly greater change from the baseline compared with the placebo group in the following indicators: IIEF-EF (9.3 vs. 1.4, $P < 0.0001$), IIEF Q3 (1.7 vs. 0.4, $P < 0.0001$) and Q4 (1.7 vs. 0.3, $P < 0.0001$), SEP2 (82.0 vs. 55.2%, $P = 0.0003$), SEP3 (68.9 vs. 22.3%, $P < 0.0001$), GAQ (76.9 vs. 19.1%, $P < 0.0001$). Normal EF domain scores (≥ 26) at the study end were achieved by 32.7% and 9.4% in the mirodenafil and placebo groups respectively ($P = 0.0031$). As for the Life Satisfaction Checklist scores, the mirodenafil group showed significantly greater improvements in sexual life and partner relationship than the placebo group. Most treatment-associated AEs were mild that resolved spontaneously. The conclusion of this study was that mirodenafil is an effective and well-tolerated agent for the treatment of diabetic patients with ED in Korea (Park et al., 2010).

Adverse events of PDE-5 inhibitors

The tolerance and safety of PDE-5 inhibitors is very good. Recent studies have even shown several pleiotropic beneficial effects of PDE-5 inhibitors in patients with CAD, hypertension, heart failure, pulmonary arterial hypertension, DM and Raynaud's phenomenon (recent reviews in Chrysant, 2013, Giagulli et al., 2013). Side effects and interactions of PDE-5 inhibitors with other drugs have been minimal, with the exception of their co-administration with nitrates, which could lead to severe vasodilation and hypotension and therefore, their co-administration is prohibited. A Cochrane Database Report analyzing the randomized placebo-controlled studies did not find any lethal case in men with DED. Only in one study have cardiovascular adverse events been reported. The most common side effects (with a decreasing rate) are: headache, flush, respiratory tract complaints and flu-like symptoms, dyspepsia, myalgia, vision disturbances and back pain (Vardi, Nini 2007).

More concise data about the adverse events are available for the "older" PDE-5 inhibitors. After a systematic review and meta-analysis (Tsertsvadze et al., 2009) the following conclusions

Drug	Dose (mg)	$t_{1/2}$ (h)	Frequency	Advantages	Side effects
sildenafil	25, 50 *, 100	4.6	On demand or daily	safe; available on demand as well as continuous low dose (tadalafil 2.5 and 5 mg)	headache, myalgia, back pain, blurred vision, facial flushing, nasal congestion, dizziness
tadalafil	2.5, 5, 10, 20	17–21			
vardeafil	2.5, 5, 10 *, 20	4–5			
avanafil	50, 100, 200	5–10			
udenafil #	100, 200	11–13			
mirodenafil #	50, 100	2.5			

$t_{1/2}$: plasma half-life time; h: hours; * also available in orodispersible formulation (supralingual); #not approved in Europe (Gareri et al., 2014; Park et al., 2014; Kang, kim, 2013; Ryu et al., 2013)

Table 2 Currently available PDE-5 inhibitors.

about (1) vs. placebo and (2) head-to-head comparisons were made: (1) A greater proportion of men treated with PDE-5i than placebo had at least 1 adverse event. The most commonly reported adverse events were headache, flushing, rhinitis, and dyspepsia. Other reported events were visual disturbances, myalgia, nausea, diarrhea, vomiting, dizziness, and chest pain. In general, these events were mild to moderate and were transient. Serious adverse events were reported in fewer than 2.0% of participants, and the incidence did not differ between PDE-5 inhibitor recipients and placebo recipients. (2) Differences in the incidence of any adverse events among men treated with sildenafil (range, 24.0–34.0%), tadalafil (range, 28.0–35.0%), and vardenafil (27.0%) were not statistically significant. Discontinuation due to adverse effects ranged from 0.5–3.8% during tadalafil treatment, 0.5–3.8% during sildenafil treatment, and 1.0% during vardenafil treatment. The frequency of specific adverse events (headache, flushing, dyspepsia, and nasal congestion) seemed similar among treatments. Data about the currently available PDE-5 inhibitors worldwide are presented on **Table 2**. In real **non-responders** to a particular PDE-5 inhibitor the following could be attempted: (1) test for low testosterone level (if not already done at the initiation of the treatment) and if hypogonadal – TRT should be started (more details in Nieschlag et al., 2006); (2) metabolic optimization (also an earlier target); (3) escalation of the dose of the PDE-5 inhibitor ad maximal; (3) change of the PDE-5 inhibitor; (4) daily dosing of tadalafil; (5) second and third line treatment.

Second and third line treatment options

Second line treatment options include intracavernosal injections of individual or combined (bimix, trimix) drugs and vacuum constrictor devices. Third-line therapy are the penile prostheses (implants).

Intracavernosal injections (ICI)

Since 1983, ICI has become a staple therapeutic option and high success rates have been reported (Coombs et al., 2012). ICI of vasoactive drugs – prostaglandin E1 (also used transurethral), phentolamine, vasoactive intestinal peptide (VIP), papaverine. PGE1 stimulates adenylate cyclase, thereby increasing levels of cAMP, which results in smooth muscle relaxation and vasodilatation. Erection appears after 5–15 min and lasts for a period that depends on the dose injected. The patient should be enrolled in an office-based training programme (requiring 1 or 2 visits) to learn the correct injection procedure (Phé, Rouprêt, 2012). Intracavernosal injections remain safe, and a highly effective treatment option in men with DED (Redrow et al., 2014). The efficacy rate is approximately 70%, with reported sexual activity after 94% of injections, and satisfaction rates are high (Moore, Wang, 2006). However, dropout rates of 41–68% have been reported, with most dropouts occurring within the first

2–3 months (Vardi et al., 2000). Complications with intracavernous alprostadil include penile pain (50% of patients after 11 % of injections), prolonged erections (5%), priapism (1%) and fibrosis (2%) (Hatzimouratidis, Hatzichristou, 2005). Drug combinations such as alprostadil plus papaverine, a non-specific PDE inhibitor resulting in increased levels of cAMP and/or cGMP, and alprostadil plus phentolamine, a competitive antagonist of alpha-1 and alpha-2 adrenoreceptors, may increase efficacy by up to 90%.

Vacuum constriction devices (VCDs)

apply negative pressure to draw blood into the penis that is then retained by the application of a visible constricting band at the base of the penis. This method appears to be more acceptable to older patients (Levine, Dimitriou, 2001). There are few recognized complications with this low-cost treatment option for selected diabetic ED patients. It was reported that VCDs achieved satisfactory erections in more than 70% of diabetic men (Price et al., 1991). Recently, Sun et al. (2014) reported that combined use of sildenafil and VCD for 3 months significantly enhances erectile function, and is well tolerated by DM patients not responding to first-line sildenafil 100 mg alone (Sun et al., 2014). Problems with VCDs include pain from the constriction ring, lack of spontaneity, decrease in the quality of orgasm and ejaculatory discomfort. In addition, up to 30% of patients discontinue use as the result of inadequate rigidity, penile pain, failure to ejaculate and the appearance of the penis while using the device (Price et al., 1991; Sidi et al., 1990).

Penile implants

When pharmacotherapy fails, surgical implantation of a penile prosthesis may be considered. Penile implants provide a predictable and reliable erection, and have the highest satisfaction rate among both patients and their partners of all the available treatments for waning erections (Phé, Rouprêt, 2012; Redrow et al., 2014). Prostheses are either malleable (semirigid) or inflatable (2- or 3-pieces). In a study of 224 Chinese men patient satisfaction was higher ($P < 0.05$) in the 3-pieces inflatable than in the malleable prosthesis group (Song et al., 2013). Men with DM are more likely to require more aggressive treatments for ED. In a recent study including 19236 diabetics it was shown that they were more than 50% more likely to be prescribed secondary ED treatments, and more than twice as likely to undergo penile prosthesis surgery compared to non-diabetics (Walsh et al., 2014). DED is among the 2 main reasons for implantation of an implant. Segal et al. (2014) developed a prediction tool based on a patient's clinical history to determine likelihood of ultimately receiving a penile prosthesis (Segal, 2014). Inclusion criteria were 18 years of age with 1 year of continuous enrollment at the first diagnosis of ED. Analyzing the data from the Commercial (N = 310303) and Medicare (N = 74315) supplemental data-

bases they found approximately 1%/N=3928 patients of the dataset's population (0.78%/2405 and 2.05%/1523, respectively) underwent penile prosthesis implantation during the study period. Factors with the greatest predictive strength of penile prosthesis implantation included prostate cancer diagnosis (relative risk: 3.93, 2.29; 95% CI, 3.57–4.34, 2.03–2.6) and DM (2.31, 1.23; 2.12–2.52, 1.1–1.37) (both $P < 0.01$).

The 2 main complications associated with penile prostheses are mechanical failure (<5% after a 5-year follow-up with the currently available 3-pieces prostheses) and infection. Since the introduction of a 3-pieces inflatable penile implant impregnated with the antibiotics minocycline and rifampin, there has been a significant reduction in infection rates and currently, the infection rate is 1% (Carson et al., 2011). The "no touch" enhancement to the surgical procedure further decreases the rate of infection to 0.46% (Eid et al., 2012). For non-impregnated implants, the infection risk rate is around 2.5% (Montague et al., 2001). Some research has indicated that diabetics have an increased risk of infection vs. non-diabetics, but most studies observed no differences in infection rates (Wilson, Delk, 1995; Jarow, 1996; Wilson et al., 1998; Montague et al., (2001); Chung et al., 2013). A penile prosthesis infection may be either treated with explantation of the prosthesis with a possible delayed reimplantation or a salvage procedure with an immediate reimplantation of the prosthesis. In a total of 1557 patients treated with an explantation only (82.7%) or salvage (17.3%) comorbid diabetes did not independently affect the salvage rate of penile prosthesis infection (Zargaroff et al., 2014).

Conclusions

Due to its complex pathogenesis DED is more common and difficult for treatment compared to healthy men. Its presentation commonly precedes the clinical manifestation of vascular diseases in other arterial areas and might be a predictor for more serious micro-vascular problems. Therapeutic schemes for comorbidities like hypertension, dyslipidemia, pain relief, psychological problems, etc., should be composed carefully and harmonized in the aspect of metabolic syndrome and ED. Treatment of DED requires a team approach, with the very important participation of specialists in sexual medicine. The therapeutic approach includes correction of metabolic disturbances and possible hypogonadism. Although effective and safe medications already exist, very often DED is not adequately diagnosed and treated which leads further to aggravation of psychological and couple distress. In most cases the reason for this is the communicative problem – the physician does not ask and the patient does not share spontaneously the presence of DED. PDE-5 inhibitors are the first line therapy in DED. Switching to second and third line therapy – intracavernosal injections, vacuum constriction devices, and penile implants is more common in men with DED.

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