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Эректильная дисфункция как проявление урогенитальной автономной нейропатии у больных сахарным диабетом 1 типа: эпидемиология, классификация, патофизиология, диагностика и методы лечения

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Нарушения половой функции, характеризующиеся значительным снижением качества жизни пациентов, приводя к бесплодию и проблемам социального характера, наблюдаются более чем у 40% больных сахарным диабетом (СД).
Наиболее распространенным нарушением половой функции у больных СД является эректильная дисфункция. В статье освещены эпидемиология, классификация, патофизиология, диагностика и методы лечения эректильной дисфункции у пациентов с СД 1 типа.
Ключевые слова: *урогенитальная диабетическая полинейропатия; эректильная дисфункция; нейрогенная эректильная дисфункция; васкулогенная эректильная дисфункция; смешанная эректильная дисфункция; ингибиторы ФДЭ-5*

Erectile dysfunction as a manifestation of urogenital autonomic neuropathy in patients with type 1 diabetes: epidemiology, classification, pathophysiology, diagnosis and treatment options

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Sexual dysfunction characterized by a significant decline in the quality of life of patients and leading to infertility and problems in social life is diagnosed in more than 40% of patients with diabetes mellitus (DM).
Erectile dysfunction is the most common sexual disorder in DM patients. The article describes epidemiology, classification, pathophysiology, diagnostic and treatment of erectile dysfunction in T1DM patients.
Keywords*: urogenital diabetic polyneuropathy; erectile dysfunction; neurogenic erectile dysfunction; vasculogenic erectile dysfunction; mixed erectile dysfunction; PDE-5 inhibitors*

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The number of patients with diabetes mellitus (DM) is progressively increasing across the world. According to the International Diabetes Federation, more than 371 million people currently suffer from diabetes. Type 1 diabetes mellitus (T1DM) accounts for approximately 10% of the total number of DM patients [1].

Sexual dysfunction is characterised by a significant decrease in patient quality of life and leads to infertility and social problems. This condition is diagnosed in more than 40% of DM patients [2, 3]. Notably, sexual disorders in T1DM patients develop at a younger age compared with the non-diabetic population [4].

Erectile dysfunction (ED) is the most common sexual disorder in DM patients. Numerous studies have shown that ED develops in 35–55% of T1DM patients [5], and the risk of ED in DM patients is three times higher than that in non-diabetic population [6].

The incidence of ED in DM patients directly depends on the patient's age, the duration of the underlying disease and the period of carbohydrate metabolism decompensation [7, 8]. In addition to all other factors, the development of ED is affected by comorbidities, DM complications and therapeutic efficacy [9]. For example, several studies have investigated the relationship between the development of ED and delayed DM complications and shown that ED is reported twice as often in patients with diabetic nephropathy and retinopathy [10].

The presence of ED in DM patients may be an indirect sign of the onset or progression of atherosclerosis and coronary heart disease, as well as the first manifestation of diabetic neuropathy [11, 12]. The results of a study conducted by R.V. Rozhivanov in the Endocrinology Research Centre (2005) were comparable with the data reported by foreign authors regarding the prevalence of ED among patients with

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type 1 and type 2 diabetes. Their data on the relationships among the prevalence, patient age and disease duration, as well as on the relationship between the level of carbohydrate metabolism compensation and the presence of diabetes complications were also similar [13].

Given the high prevalence of ED in type 1 diabetes mellitus and the general understanding that this condition not only reduces the quality of life of young patients but also represents a symptom of DM complications such as diabetic neuropathy, IHD and atherosclerosis, it is necessary to develop a timely, personalised and comprehensive approach for the diagnosis and treatment of ED in this category of patients.

CLASSIFICATION OF ERECTILE DISFUNCTION

The classification of ED is based on aetiology and pathogenesis.

Forms of ED:

- organic (vasculogenic, neurogenic, and endocrine);
- psychogenic;
- mixed (organic pathology and psychological factor);
- drug-related.

The functional status of the penis is regulated by the tone of the smooth muscles in the blood vessels and trabeculae of the corpus cavernosum. Sexual stimulation leads to the production of nitric oxide (NO) after nervous and endothelial activation, in turn increasing the concentration of soluble guanylate cyclase (GMP). The increasing concentration of cyclic GMP (cGMP) results in the relaxation of the smooth muscle fibres, heightened arterial inflow and penile veno-occlusive insufficiency. The rate of cGMP decay depends on the activity of phosphodiesterase type 5 enzyme [15].

In DM patients, the development of ED may be caused by multiple factors (atherosclerosis + neuropathy, neuropathy + psychogenic factors, etc.) [14].

Penile erection is regulated by different isoforms of NO synthase that are of neuronal, endothelial and smooth muscle origin [16]. There are several biochemical mechanisms that can explain the onset of ED in DM patients. A combination of vascular and neuropathic components may cause ED in DM patients. It is known that endothelial dysfunction leads to the development of ischaemic neuropathy, which, in turn, has a detrimental effect on NO synthesis. Numerous studies have demonstrated the disruption of the endothelium-dependent and neurogenic relaxation in the corpora cavernosum of DM patients with ED. This finding is associated with NO deficiency. Furthermore, some foreign studies have demonstrated a significant increase in the number of NO synthase-binding sites in the corpora cavernosa tissues of rats two months after the induction of diabetes mellitus [17]. The aforementioned process is similar to those reported for other vascular beds, which found that the endothelium-dependent relaxation of the vascular wall is affected by the disruption of NO synthesis by high concentrations of glucose. Therefore, the distortion of NO-synthase activity plays a role in the aetiology of ED in DM patients due to diffuse endothelial dysfunction [18]. It has also been shown that the relaxation of the smooth muscle cells in the corpora cavernosa of DM patients by electrical stimulation is weak due to the lower production of nitric oxide by NO synthase. Moreover, prolonged hyperglycaemia induces an increase in the uptake of nicotinamide adenine dinucleotide phosphate (NADPH), a cofactor in the NO production, reducing nitric oxide levels [19].

The excessive generation of free radicals affects NO-induced relaxation through the accumulation of advanced glycation end-products (AGEs) circulating in the blood; AGE are also responsible for the development of diabetic vascular complications [20].

AGE-products, which accumulate in the DM patients, have been shown to interact with specific receptors in tissues that demonstrate vascular lesions.

AGE products increase the expression of the mediators of vascular lesions, the release of which is also stimulated by glucose [21, 22, 23].

In addition to all other options, the mechanism responsible for vascular lesions in DM patients involves the induction of plasminogen activator inhibitor-1 and changes in the gene expression of adhesion molecules and P-selectin [24, 25].

All of these factors are involved in the pathophysiology of cardiovascular diseases, which are characterised by high mortality (silent myocardial ischemia, sudden cardiac death, etc.) and are strongly associated with ED [26].

Neuropathy is an important stage in the development of diabetic ED. It has been shown that DM patients with ED have morphological damage in the autonomic nerve fibres in their corpus cavernosum tissue [27]. Peripheral neuropathy is considered to be typical for patients with ED; however, the decrease in nerve conduction velocity and heart rate variability was slightly more frequent in patients with DM and ED than in patients with ED and polyneuropathies of different origins [28].

Numerous studies describing the pathological changes in the nervous system of DM patients have reported that the primary lesions of the peripheral nerve fibres are independent [29].

Autonomic neuropathy seems to be the major ED pathogenetic factor in DM patients. It has been shown that patients with manifestations of peripheral neuropathy are more likely to suffer from ED than DM patients without polyneuropathies [30]. The most popular metabolic hypothesis is the polyol exchange theory, which suggests that, in DM patients, an excess of glucose is metabolised via the polyol pathway and is ultimately converted to sorbitol and fructose; this accumulation in the nerve cells triggers the development of neuropathy. [31] The significance of hyperglycaemia in the development of diabetic neuropathy is clinically confirmed by the fact that proper carbohydrate metabolism compensation reduces the progression of diabetic neuropathy by 40–60% [32].

Other findings have also supported the vasculogenic hypothesis of the development of neuropathy via the depletion of endoneurial blood flow, increasing endoneurial vascular resistance and reducing nerve oxygenation. According to this theory, the pathological changes in the

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endoneural vessels and the associated hypoxia and ischaemia are the primary factors [33].

All of the facts mentioned above indicate the important role of peripheral neuropathy in the development of ED in DM patients. Many authors describe this condition as 'neurogenic ED', thus drawing attention to the leading role of diabetic neuropathy in the erectile disorders of these patients [31, 34].

In addition to the neurogenic and vasculogenic forms of ED, endocrine ED associated with androgen deficiency is also quite common among DM patients [35].

NO synthase has recently been found to be an androgen-dependent enzyme [36], as substantiated by the fact that the neuronal cells of the parasympathetic pelvic ganglia have androgen receptors that produce NO and vasoactive intestinal polypeptides [37]. This observation has been further confirmed by the stimulation of NO synthesis in the ganglia under the influence of androgens. [38] Notably, hypogonadism is a common symptom in DM patients [39]. The causes of androgen deficiency in men with diabetes vary, including being overweight or obese and age-related declines in testosterone secretion [40].

DIAGNOSIS OF ERECTILE DISFUNCTION IN DIABETES MELLITUS PATIENTS

A classical scheme of patient examination is used to diagnose ED comprising the collection of medical history, a physical examination, and laboratory and instrumental methods.

The key points in the collection of a medical history for DM patients involve assessing the progression of the underlying disease, the presence or absence of DM complications and information on the prescribed medications.

Body mass, height and body mass index are recorded during the physical examination because excessive weight may lead to hypogonadism. In some cases, it makes sense to perform a differential assessment of the visceral fat content by CT scanning in order to achieve a more accurate assessment and risk prediction. In addition, the state of the skin, the nature and intensity of the body hair and the state of the musculoskeletal system and genitals are assessed [41, 42].

A certain minimum of neurological diagnostic methods must be employed during the physical examination to diagnose neuropathy. The most informative of these is the evaluation of the bulbocavernosus reflex [43]. Evaluation of the temperature, tactile and vibrational sensitivity of the penis can also be recommended [44].

The range of special diagnostic procedures for patients with ED include a hormone blood test, penile tumescence monitoring during the night, intracavernous pharmacodynamic study, cavernosography, angiography of penile blood vessels, Doppler ultrasound study of the penile blood vessels and the determination of the nerve conduction velocities in n. pudendus [45].

All of the aforementioned examination methods are used to diagnose ED of any origin; however, electroneuromyography is the most informative method and the only one currently used to diagnose the neurogenic form of ED in DM patients. The list of tests that can assess the status of sensory and efferent fibres includes perineal electromyography of the latent bulbocavernous reflex, hidden sacral test, dorsal somatosensory evoked potential test and vibrational study of perceptual sensitivity. In DM patients with ED, the results of these tests usually deviate from normal values. For example, an increase in the latent bulbocavernous reflex is typical of DM patients [43]. However, the aforementioned tests do not reveal information on the state of the efferent autonomic innervation, which is responsible for penile erection. Based on the above facts, a deviation from the normal test values alone can suggest autonomic neuropathy in the penis [46].

Registration of the electrical activity of the cavernous smooth muscle using an intracavernous needle or surface skin electrodes can be employed to directly study cavernous autonomic innervation. The data obtained using this method allow one to evaluate the status of the neuro-reflex functions of the penis and to identify disorders at the level of corpora cavernosa and interactions at the nerve endings. In the study of autonomic cavernous innervation in DM patients, irregular potentials with low amplitudes and a slow rate of depolarisation were observed. Desynchronisation is also typically noted in a paradoxical increase in the activity of the cavernous tissue in response to the administration of vasoactive drugs, whereas no action potentials are observed in healthy subjects after the intracavernous administration of vasoactive drugs [47].

The available data are insufficient to establish the specificity and sensitivity of this method.

Based on these findings, it becomes apparent that the actual diagnosis of the neurogenic form of ED in DM patients is a challenging task, especially because no highly sensitive or specific method for its diagnosis exists today. It is also necessary to keep in mind that erectile dysfunction is often the first symptom of developing neuropathy. The neurogenic form of ED in DM patients can be assumed based on the presence of other manifestations of diabetic neuropathy (decreased body temperature, vibrational and pain sensitivity, various manifestations of the cardiovascular and gastrointestinal forms of autonomous diabetic neuropathy, unrecognised hypoglycaemia). The data supporting the presence of vascular insufficiency and hypogonadism, along with complaints of erectile disorder, may also be indicative of neurogenic ED.

TREATMENT OF ERECTILE DISFUNCTION IN DIABETES MELLITUS PATIENTS

A personalised approach is required when choosing ED treatment for each DM patient [45]. Because DM patients may have specific complications, the choice of methods

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for treating ED ought to be justified [48]. It is well known that pharmacological methods are the treatment of choice for ED, but more importantly, a stable compensation of the carbohydrate metabolism must be achieved in order to obtain an effective ED therapy.

Currently, there are several methods of local treatment for ED, including vacuum therapy, intracavernosal and transurethral pharmacotherapy. All of these methods have certain drawbacks that limit their use in DM patients. For example, each is associated with possible damage to the soft tissues in cases of intracavernous pharmacotherapy or to the urethral mucosa in cases of transurethral pharmacotherapy. These effects are undesirable in DM patients due to their high risk of infection at micro-injury sites [45].

Phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, tadalafil, udenafil) are currently the drugs of choice for treating ED. Drugs of this class are modulators of erectile function. They selectively inhibit the PDE-5 enzyme without exerting a direct effect on the smooth muscle cells of the penis and increase the effect of NO, which is synthesised in response to sexual stimulation. Thereby, they strengthen the physiological processes responsible for the onset and maintenance of erections in response to sexual stimulation [45].

Years of experience with sildenafil in DM patients have demonstrated its high efficacy in treating ED [45, 49]. This observation has also been confirmed by long-term studies, the results of which suggest the possibility of the long-term, safe, and effective use of the drug without dose escalation [50].

The efficacy of vardenafil for treating ED in DM patients has been studied in a multicentre, double-blind, placebo-controlled study of 452 patients. After 12 weeks, improved erections were observed in 52 and 72% of the patients who received 10 and 20 mg of vardenafil, respectively, whereas improved erections were observed in only 13% of the patients in the placebo group [51].

Fonseca et al. (2006) studied the efficacy and safety of tadalafil in men, including DM patients, in a meta-analysis of 12 placebo-controlled trials in ED patients, with and without diabetes. The studies included 1,681 non-diabetic men and 637 men with type 1 and type 2 diabetes, respectively, who received tadalafil at doses of 10 and 20 mg or placebo for 12 weeks. DM patients had a more pronounced ED compared to patients without diabetes. The ED scale (IIEF) score was inversely correlated with the HbA_{1c} level. Compared with placebo, tadalafil at doses of 10 mg and 20 mg significantly improved ED in both groups and improved the quality of life. The efficacy of tadalafil was independent of the degree of carbohydrate metabolism compensation or DM therapy received by a patient. Thus, despite the more severe ED in DM patients, tadalafil was effective and well-tolerated [52]. Tadalafil has a longer elimination half-life (17.5 hours), providing a significantly longer duration of action and restoration of the natural character of sexual relationships [53]. The patient gets a chance to lead a normal sexual life, which is extremely important in light of the additional psychogenic factors that can complicate the course of ED in DM patients [54].

However, according to the same researchers, PDE5 inhibitor therapy is ineffective in 20–40% of patients with ED. In some cases, this inefficiency is associated with androgen deficiency; therefore, it may be appropriate to prescribe a combination therapy of androgen drugs and PDE-5 inhibitors to patients displaying the aforementioned clinical signs at the time of the diagnosis in order to increase the therapeutic effectiveness to 93% [55, 56, 57].

The use of PDE-5 inhibitors to treat sexual dysfunction in DM patients may also have the added benefit of reducing the symptoms of genital neuropathy [49].

For example, a study of sixteen 27-year-old men with T1DM and ED [25, 29] with penis shaft paresthesia and impaired sensitivity of the glans who received a PDE-5 inhibitor over 3 months revealed the complete elimination of ED in all patients (ED score 21 for those who received therapy [21, 22], $p < 0.001$) and the normalisation of spontaneous erections. A statistically significant decrease in the number of complaints typical of genital neuropathy and an improvement in the temperature sensitivity of the penis were also noted. [49]

It should be noted that a neuroprotective effect of PDE5 inhibitors has been observed in diabetic neuropathy. G. Hackett described five clinical cases in which patients with painful distal diabetic neuropathy reported a significant reduction in symptom severity after the regular administration of PDE5 inhibitors. The benefits of PDE5 inhibitors may be explained by their effects on endothelial function, as they improve blood flow in the *vasa nervorum* [58].

Drugs based on alpha lipoic (thioctic) acid [59] are the most promising ones for the treatment of painful diabetic polyneuropathy. Several foreign and one Russian study, although not placebo-controlled, demonstrated the efficacy of these drugs for the treatment of both diabetic polyneuropathy overall and neurogenic ED in particular. It should be noted, however, that this effect was short-term and dependent on the time of intravenous infusion [60].

Unfortunately, despite the fairly wide range of tools for the conservative treatment of ED in T1DM patients, for one group of patients, they are ineffective. In this case, a surgical intervention consisting of a penile prosthesis implantation should be prescribed.

CONCLUSION

The relatively high prevalence of ED in young DM patients and the impact of ED on the psychological state of these patients and their overall quality of life make this condition a serious problem.

The data shown above make it clear that physicians currently have at their disposal a wide range of different methods for diagnosing ED; however, no highly specific and sensitive method for diagnosing the neurogenic form of ED has been developed at present. It is important to consider that a timely diagnosis with the correct determination of the type of ED can be used as a basis for reasonable and careful therapeutic choices for each patient.

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ED treatment in T1DM patients should be comprehensive and aimed not only at improving the erectile function itself but also at eliminating the pathogenic factors of ED development, such as chronic hyperglycaemia, dyslipidaemia and androgen deficiency. Currently, pharmacological therapy is the method of choice; PDE5 inhibitors occupy the top spot due to their high efficacy, safety and simplicity of use for patients. It should be noted that this class of drugs has neuroprotective properties, which is especially important for those patients with a neurogenic form of ED. Still, this issue requires further in-depth research.

Therefore, despite great advances in the development of methods for diagnosing and treating ED, there are still many unresolved issues that require further investigation.

DISCLOSURE INFORMATION

The authors declare no conflicts of interest in connection with the writing of this article..

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